

THE BASIS OF CHEMOTHERAPY

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BY

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OLIVER AND BOYD LTD.

EDINBURGH: TWEEDDALE COURT

LONDON: 98 GREAT RUSSELL STREET, W.C.

1948

TO
THE LATE
GEORGE BARGER
TEACHER AND FRIEND

PRINTED IN GREAT BRITAIN BY
OLIVER AND BOYD LTD, EDINBURGH

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PROLOGUE

CHEMOTHERAPY, as its name implies, is a hybrid subject. Its boundaries stretch from organic chemistry, through biochemistry and physical chemistry to bacteriology, pharmacology and therapeutics. Because of the breadth of its field, we considered a book on chemotherapy covering several of these aspects might be a useful contribution to a rapidly developing subject. Although therapeutic use of any chemical might be regarded as chemotherapy, it is usual, in practice, to restrict the meaning of the term to the chemical treatment of diseases of microbial origin with a view to eliminating the microbial infection. Such a restriction has been adhered to in this book.

We have attempted to weld many diverse sciences into a single framework in order to find a basis for chemotherapy. In so doing, we must inevitably cover ground familiar to specialists in each field. The trained organic chemist may regard our exposition of chemical theory as superfluous, the expert microbiologist may consider that we have included unnecessary fundamentals of bacteriology, while the specialist in biochemistry may feel that we have wasted space in a detailed account of enzymology and cell physiology. It has been our aim, however, to provide a sufficient background to each subject so that the student of chemotherapy may be lured into the study of subjects outside his own original field.

The history of chemotherapy during the last half century is largely one of painstaking development by the organic chemist of chance observations made by the experimental pathologist or the microbiologist. Only those who have played a part in this development can realise the immense effort that has gone towards the perfection of clinically useful drugs. In seeking a theoretical basis for our subject, we may seem to have done less than justice to this aspect, but it is already covered by standard works. The theoretical developments with which we are concerned provide no royal road to

the production of new chemotherapeutic drugs, but they begin to provide a rationale for the whole subject. If this book does something to focus attention upon the modes of action of drugs rather than upon the synthesis of ever more variants on their chemical structure, it will, to some extent, have fulfilled its purpose.

We ask the indulgence of those more expert than ourselves; we are amateur authors with a limited fund of time and energy available after full days at the laboratory bench. We should be grateful, therefore, if our colleagues would draw our attention to any obscurities or inaccuracies so that we may subsequently rectify them.

ACKNOWLEDGMENTS

OUR thanks are due to many good friends for their helpful criticism, especially to Dr C. R. Harington, Dr H. King, Dr A. T. Fuller and Dr B. C. J. G. Knight who spared the time to read our manuscript in full. Many obscure journals and references were traced for us through the cheerful co-operation of Miss Wigmore, librarian at the National Institute for Medical Research.

We were guests, during the early stages of the preparation of this work, at the schools of Biochemistry and Parasitology, Cambridge, and we particularly wish to thank Professor D. Keilin for his encouragement and help during that time.

The Medical Research Council and University College Hospital Medical School have provided the facilities without which this book could not have been produced. Many authors have helped us by granting permission for the use of material from their published work. Our publishers, Messrs Oliver & Boyd, have made our task easier by their co-operation and the care with which they printed the text.

We are indebted to the following publishers, journals and learned societies for permission to reproduce material:—Longmans Green and Co., H. K. Lewis & Co., Blakiston Co., Messrs Duckworth, Williams and Wilkins Co., Academic Press Inc., Interscience Publishers, University of Chicago Press, Journal of Biological Chemistry, Science, Journal of Experimental Medicine, Journal of the American Chemical Society, Journal of the Society of Experimental Biology and Medicine, Physiological Reviews, Journal of Infectious Diseases, Journal of Bacteriology, Journal of Pharmacology and Experimental Therapeutics, American Journal of Medical Sciences, Genetics, Royal Society, Biochemical Society, Faraday Society, New York Academy of Sciences, The Missouri Botanical Garden.

The Microbe is so very small
You cannot make him out at all,
But many sanguine people hope
To see him through a microscope.
His jointed tongue that lies beneath
A hundred curious rows of teeth ;
His seven tufted tails with lots
Of lovely pink and purple spots,
On each of which a pattern stands,
Composed of forty separate bands ;
His eyebrows of a tender green ;
All these have never yet been seen—
But Scientists, who ought to know,
Assure us that they must be so . . .
*Oh ! let us never, never doubt
What nobody is sure about.*

H. BELLOC.

CHAPTER I

HISTORICAL INTRODUCTION

Traditional remedies

(THE art of chemotherapy is as old as civilisation ; the science of chemotherapy is the child of to-day.) Treatment of disease has always been associated with administration of medicines ; while many of these were worthless and overlaid with superstition and magic, others were of real value, recognised no doubt by acute observation following a process of trial and error. To-day a more scientific basis for the use of certain of these medicines has gradually developed through the systematic isolation and testing of their active principles.

(In the East, particularly in China, herbal remedies have been in use for more than five thousand years. About 3000 B.C. the Emperor Sheng Nung recorded many of the known remedies in the Book of Herbs. Even now, the curative value of many of these has not been scientifically investigated, but in some cases the active principles have been isolated and their therapeutic value established. The plant Ma Huang, of the ephedra species, was noted by Sheng Nung to be a diaphoretic and circulatory stimulant. In 1887 the alkaloid ephedrine was isolated from the plant by Nagai, but its therapeutic value was not recognised until after 1923, when Chen showed that a decoction made from Ma Huang produced an effect on blood pressure similar to that of adrenaline (Chen and Schmidt, 1923). The drug Ch'ang Shang was also included in the Book of Herbs where it was stated to be valuable against malaria paroxysms and similar fevers. The antimalarial action of an extract of Ch'ang Shang has recently been confirmed and the active alkaloid identified (Tonkin and Work, 1945 ; Koepfli, Mead and Brockman, 1947).

Many other traditional remedies have yielded active principles which are still in use to-day. The fruit of the Kalaw or chaulmoogra tree was used by the ancient Hindus for the

cure of leprosy. An oil from the seed, chaulmoogra oil, was introduced into Western medicine in 1854 by Mourat, and is still used extensively in the treatment of leprosy. The anthelmintic, oil of *chenopodium*, from the tree *Chenopodium anthelminticum*, was probably used by the Aztecs as well as by Eastern civilisations, as is indicated by the two names, Jerusalem Oak and Mexican Tea. Male fern was esteemed by the Greeks and recommended by Theophrastus, Pliny and Galen ; while the plant *Artemisia maritima*, which has yielded the anthelmintic drug *santonin*, was known to Greek, Roman and Arabic medicine. *Ipecacuanha* root was introduced in 1658 by Guillaume le Pois into Europe from Brazil, where its medicinal qualities in curing diarrhoeas were known to the natives. The root is also said to be an ancient Indian and Chinese cure for chronic dysentery. An alkaloid, *emetine*, isolated from *ipecacuanha* by Pelletier and Magendie in 1817, was shown by Tull Walsh in 1891 to be active against amoebic dysentery.

Other valuable plant products were known to the ancient civilisations of South America. The Spanish conquest of these countries in the sixteenth century led to the introduction into Europe of several drugs believed to have been in use by the natives before conquest. *Cinchona* bark, originally known as Jesuit bark, was brought to Spain in 1633 by the Jesuits, who are supposed to have been told by Peruvian natives of its curative properties for fevers. The first record of its use has been found in the writings of an Augustinian monk, Antonio de la Calancha, who stated in 1633 that the bark of the "fever tree" cures "the fevers and tertianas; it has produced miraculous results in Lima." Tradition tells that the Countess of Chincon, wife of the Viceroy of Peru, was cured dramatically of a malarial fever in about 1630; also that the name "*Cinchona*," introduced by Linnæus for the plant genus, was suggested by her title. Recent research (Haggis, 1941) has, however, shown that this particular lady died before her husband went to Peru, and that the second wife never contracted a fever during her husband's stay there. The Viceroy himself was much troubled

with fevers which were treated by traditional bleeding methods but he was never cured by administration of any kind of drug. The alkaloid quinine, which was isolated in 1820 from cinchona bark by Pelletier and Caventou, has been, up till recently, the most effective cure known for malaria.

(Growth of European medicine

European medicine may be said to have been founded by Hippocrates in the fourth century B.C. Later, Galen (A.D. 131-200) established a formal system of medicine which persisted practically unchanged for 1500 years. Galen believed that a state of bodily health was preserved by the presence in their proper proportions of the four humours—heat, cold, dryness and moisture. Disease was supposed to result from a disturbance of the balance of these humours and could be cured by administration of various drugs possessing these fundamental qualities. Galen rejected the use of simple metallic remedies such as mercury, which seem to have been used at that time, and introduced a complicated system of therapeutics based upon herbal remedies.)

Bound by Galen's formidable mixtures, European medicine suffered a long period of stagnation which was not relieved until the sixteenth century when a fresh spirit of inquiry became evident. (Galen's doctrines were largely modified by the teachings of Paracelsus (Theophrastus von Hohenheim, born 1493). Much of Paracelsus' medical theory was overlaid with a nonsensical mass of astrology, mysticism and alchemy, but he ridiculed the absurd mixtures of herbs advocated by Galen's followers, and substituted some simple and powerful remedies, many of them metallic. He believed that there was a specific remedy for each disease, and was able to contribute one specific to medicine—namely, mercury for syphilis. This cure had been in use sporadically for some time, and its successful application by Paracelsus did much to popularise his other mineral cures, such as antimony.

Unfortunately these metallic medicines (tartar emetic, calomel, etc.) became over-popular. They are mostly highly poisonous, and it is probable that over-dosage with this type

of drug was responsible for much additional sickness and suffering. Antimony, in particular, seems to have enjoyed much popularity in the sixteenth century. The metal was used to make goblets in which wine was allowed to stand until it had acquired emetic properties, and everlasting pills of the metal were administered and recovered for future use after they had fulfilled their function. In 1566 the doctors of Paris decided, not without considerable opposition, that antimony was a poison, not a remedy, and its use was banned by Act of Parliament. However, in 1657, Louis XIV-- was treated with antimony for typhoid fever, and, as a consequence of his recovery, antimony was restored to the pharmacopœia.

In addition to metallic remedies, European medicine boasted, until fairly recently, a strange array of drugs; pearls, musk, crocodile dung, unicorn's horn, Egyptian mummy, sarsaparilla and many other strange substances were used in decoctions. The moss scraped from the skull of a criminal who had hung in chains, known as "usnea," was endowed with remarkable curative properties: it was an official drug in the pharmacopœia until the nineteenth century.

Although the seventeenth century saw the Spanish introduction into Europe of cinchona bark as an antipyretic and also of ipecacuanha, conservative medical groups viewed the new drugs with suspicion because their use did not conform to the teachings of Galen. Others looked upon cinchona with equal suspicion because the Jesuits sold it. The first official recognition came in 1677 when cinchona bark was included in the London Pharmacopœia under the title "*Cortex Peruanus*." Ipecacuanha evidently obtained popularity as a cure-all, for it is included in the famous diaphoretic "Dover powders" compounded by the buccaneer physician, Dr Dover (1660-1742).

(*Germ theory of disease*

By the beginning of the nineteenth century, a certain amount of scientific method was being introduced into medicine, and doctors were learning to assess by experiment

whether a drug was of value in curing a certain disease.) This led to elimination of many useless drugs, but not to introduction of new ones. (For this to take place on anything except an empirical basis, it was first necessary for the cause of disease to be understood.)

(The germ theory of disease was not established until the middle or late nineteenth century.) Its forerunner was a theory of the contagious nature of disease propounded in 1546 by Girolamo Fracastoro of Verona. At this time, disease was considered to be due either to divine displeasure or to elemental causes, such as comets, earthquakes, floods or changes in the air. Malaria, known as "shivering ague," was, for example, attributed to a nocturnal "miasm." Fracastoro explained contagion by postulating the existence of seeds of disease which were capable of being propagated from one individual to another. Propagation occurred by direct contact, by contact with fomites (objects which conserve the seeds), or at a distance. He gave accurate descriptions of Italian epidemics of typhus, plague, rabies and syphilis, and produced a valuable account of the general therapy of contagions. His work was held in the highest repute during his lifetime, but by the end of the sixteenth century it had been forgotten, and all that Fracastoro had achieved had to be rediscovered in the nineteenth century.

(The first proof that disease of any kind is associated with living micro-organisms resulted from work on silk-worms, published by Agostino Bassi of Lodi in 1835. He demonstrated the existence of transmissible pathogenic micro-organisms which caused the silk-worm disease *mal del segno*, and propounded a theory of contagion in such human diseases as syphilis, variola, typhus, plague and cholera. He also wrote on the destruction of germs by heat and chemicals. (Study of anthrax by various investigators, notably Davaine, between 1850 and 1865, provided the first scientific proof of the association of disease in animals with micro-organisms.) The work concluded with a statement by Davaine that bacteria are the cause of anthrax. This was confirmed and firmly established by Pasteur, who, after successive subculture of

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(*Germ theory of disease*

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isolated and characterised. Even the origins of protozoal diseases were recognised, the malaria parasite being described by Laveran in 1880. It was at this time that the science of chemotherapy was conceived. The thoughts of investigators in bacterial medicine naturally turned to methods of destroying bacteria by drugs after they had invaded the host, as well as by disinfectants outside the body.) It is interesting that the first experiments on chemotherapeutic treatment should have been made by the investigator who did so much to establish bacteriology. (In 1881 Koch infected guinea-pigs with anthrax bacilli, and treated them with subcutaneous injections of a solution of mercuric chlorido, used because of its powerful *in-vitro* bactericidal action on micro-organisms. The animals died of anthrax in forty-eight hours, in spite of dosage, both before and after inoculation, of an amount of mercuric chlorido sufficient to prevent all bacterial growth in broth.

This pioneer experiment showed at once one of the main difficulties still encountered to-day in chemotherapy: namely, substances which are highly active against micro-organisms *in vitro* are often ineffective *in vivo*.) Even before Koch's experiment, an indication of this difficulty had appeared; Baxter (1875), using vaccine lymph and glanders nodules, showed that organic matter diminished the activity of disinfectants. We now know that many disinfectants are adsorbed by proteins, so that the uptake of disinfectant by the proteins of host blood and other cells diminishes the amount available to combat infecting organisms.

(Effect of dyes on tissues and micro-organisms)

The important subject of distribution of drugs in the body was continually stressed by Ehrlich, father of the science of chemotherapy. Ehrlich's first work was on the distribution of dyestuffs in the animal body (summarised, 1885.) His interest in this field was aroused, when he was a student, by a paper on lead poisoning, by Heubel, claiming that organs in which lead accumulated could also fix the metal from solution after death. Ehrlich was led from this work to

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the organism, produced a culture which still infected susceptible animals. This technique, introduced by Pasteur, enabled him to show that any non-viable material carried into the primary culture from blood or tissues would be too highly diluted during subculture to be responsible for the infective nature of the final culture.

(At this time Pasteur also established that yeasts are the causative agents of fermentation in wine and other organic solutions). In 1861 he published his work disproving the theory of spontaneous generation of micro-organisms, a favourite subject of controversy among biologists. He also developed methods for the isolation and cultivation of bacteria, for the study of their effects on animals, and for the passage of a virus disease, such as rabies, through an animal.

(In 1865 Lister successfully applied the principles of Pasteur's germ theory to surgery, and established that, by cleanliness and sterilisation of wounds with phenol, the dreaded and all too common putrefaction of wounds could be prevented. The success achieved by Lister in the development of his antiseptic system of surgery did much to make the germ theory acceptable to the medical profession. Further work by Davaine in 1872 on septicæmia suggested that sepsis was bacterial in origin, since a rabbit could be killed by injection of an amount of blood from an infected rabbit corresponding to one-billionth of a drop. (The question was finally proved by Koch in 1878 when he demonstrated that six different infective diseases could be induced by injection of "putrid" fluids into animals.) Koch perfected bacteriological techniques introduced by Pasteur, and applied staining techniques and oil immersion to the microscopic study of bacteria. His first work in 1876 was a remarkably complete description of anthrax bacilli and spores, and their methods of dissemination in animals.

(The establishment of the germ theory of disease and the perfection of bacteriological techniques opened up a new era in medicine. Advances in all fields were extremely rapid, and during the last twenty years of the nineteenth century micro-organisms responsible for many infective diseases were

oxygen of these side-chains was assumed to vary in different organs. Here we find the germ of Ehrlich's side-chain theory on which he later based his chemotherapeutic theories.

It was natural at a time when new developments were continually being made in bacteriology, that Ehrlich should turn his attention to staining of bacteria. In 1881 he found that bacteria as well as tissues were stained by methylene blue. In 1882 he developed an acid-fast stain for tubercle bacillus which is the essence of the Ziehl-Neelsen staining method used to-day, and which consists of an aniline-water solution of methyl violet or other aniline dye, with vesuvin or methylene blue as a counter-stain. This aniline-water methyl violet mixture of Ehrlich was also used by Christian Gram (1884) in the now universally known "Gram stain." The Gram process of staining has divided bacteria into two groups, Gram-negative and Gram-positive, according to whether they retain the aniline dye after suitable treatment. This grouping is also found to divide bacteria according to their susceptibilities to the action of bacteriostatic agents, basic dyes, detergents and antibiotics. Gram-positive organisms are attacked under normal conditions by such agents. Gram-negative organisms are frequently more resistant, but are more susceptible to enzymic digestion and to lysis by immune serum in the presence of complement. Henry and Stacey (1942, 1946) showed that the fundamental difference between Gram-positive and Gram-negative organisms is related to the presence in Gram-positive organisms of a magnesium ribonucleate which can be separated from the "cytoskeleton" by suitable extraction methods. The "cytoskeleton," which is Gram-negative, can be recombined with magnesium ribonucleate and then stains Gram-positive once more.

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believe "that the ways and means by which drugs are distributed over the body must be of the greatest importance in the rational development of therapeutics" (Ehrlich and Hata, 1911). Accordingly, he examined the distribution of dyestuffs, first in blood, and next in living animals. Dyestuffs were chosen because of the obvious ease in following their distribution. An early result of this work was the differentiation and classification of various types of body cells, particularly blood leucocytes. Following this, Ehrlich carried out his well-known experiments on vital staining. On killing an animal some time after injection of methylene blue, he found that the only tissues dyed were those of the nervous system, all the nerves being sharply defined along their whole length. By the use of many different dyes, he found that certain dyes stained specifically certain organs or types of cells, while others were fairly general in their action. For example, many basic dyes such as Bismark brown, neutral red, flavanilin or methylene blue stained nerve tissue only, while only one acidic dye, alizarin, had this property. These so-called "neurotropic" dyes lost this property on conversion to sulphonc acid derivatives. These facts were explained by Ehrlich by assuming that acidic dyes are bound in the blood by the alkali present, while basic dyes are not held in blood by any chemical affinities and are thus freer to diffuse into surrounding tissues. He emphasised that similar differences in distribution of colourless substances in the body are likely to occur.

Other interesting results of the study of vital staining were series of experiments on the oxygen requirements of organs. After injecting either alizarin blue or indophenol in the colloidal state into the circulation of an animal, Ehrlich found, on killing the animal, that some organs were coloured blue, while other organs had reduced the dye and contained the colourless leuco product. Organs which ordinarily did not reduce the dye, did so when a state of asphyxia was established. From this work he deduced the relative combining powers for oxygen of different tissues. The results were explained on the supposition that in cell protoplasm side-chains existed whose function was oxygen fixation; the affinity for

oxygen of these side-chains was assumed to vary in different organs. Here we find the germ of Ehrlich's side-chain theory on which he later based his chemotherapeutic theories.

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recorded by Stilling (1890), who obtained inhibition of growth of certain bacteria with dilutions of dye of 1 in 2,000,000. He concluded that aniline dyes, in sufficient concentration, will prevent the development of practically all bacteria. Stilling also propounded a theory for the mode of action of dyes which is interesting in the light of modern conceptions of germicidal action. He observed that when micro-organisms were first placed in solutions of dyes, the dye was deposited in the intermicellary spaces of the covering membrane, which was thereby stained; from these it could be extracted merely by placing the cell in water. This occlusion in intermicellary spaces, even without chemical combination, was considered to be sufficient to affect the metabolism of the cell so as to cause serious consequences to the organism, but not its death. On longer exposure, or in the presence of a greater concentration of dye, a certain amount of dye penetrated into the cell protoplasm where it may have existed as in the cell membrane, and from which it could also be extracted with water. Death of the cell resulted only when still longer exposure or still higher concentration of dye caused increased storage in the protoplasm, in consequence of which "the vital movements of the plasmatic micellæ are arrested." In this case the dye could no longer be extracted with water. This work was further extended by experiments on infections in animals, and Stilling recommended that a mixture of blue dyes known as "pyocetanin" should be used for the treatment of minor surgical infections, as it was non-toxic to animal tissues.

(In 1891 Ehrlich performed his first experiment in chemotherapy. He found that methylene blue stained malaria parasites very effectively, a result which induced him, in collaboration with Guttman, to try the dye on malarial patients. Some success was obtained: cases of tertian malaria were cured by administration of methylene blue, but the results were not sufficiently impressive to warrant the substitution of methylene blue for quinine. We shall see later, however, that this work played a guiding part in the development of the antimalarial drugs plasmoquine and atabrin.)

Knowledge of disease at the beginning of the twentieth century

Ehrlich started his intensive work on chemotherapy in 1902. Before considering this work, it may be helpful to review the extent of knowledge at that time regarding cure and prevention of disease. The causative agents of most infective diseases, with the exception of virus diseases, were by then known. Experimental transmission of bacterial infection in laboratory animals was possible, as was the isolation and maintenance of pure strains of bacteria. The bactericidal action *in vitro* of phenolic compounds and dyes was known, and a fairly reliable method of standardising bactericidal action was achieved in the Rideal-Walker test (Rideal and Walker, 1903). Bacterial immunity was well known and serum therapy was established as a means of curing disease.

Ehrlich himself had made a major contribution to immunological work, which culminated in his theory of immunity published in 1897. He continually emphasised the chemical side of immunology, seeking to prove that the interaction between toxin and antitoxin was a chemical one and not, as was held by others (Bordet, 1903), due to physical forces. We have already mentioned that Ehrlich considered protoplasm to contain a grouping responsible for the fixation of oxygen. He also believed that protoplasm contained numerous other "receptors" whose normal function was to anchor by chemical combination a variety of foodstuffs as a preliminary step to their incorporation into the cell substance. The theory of immunity was an extension of this idea. The toxins (or antigens) combined with the specific receptors in the cell, just as the food molecules were supposed to do; but since the toxins were foreign substances not concerned in the normal economy of the cell, the receptors in question were diverted from their normal function. The cell was stimulated to replace these useless receptors, and in making new ones, formed an excess which was finally thrust off into the blood. The excess receptors in the blood constituted the specific antitoxin or antibody. This theory, now known to have many failings, had the merit that it kept to the fore the important

point that chemical specificity is an essential feature of immunological reactions. It also formed a basis for Ehrlich's views on chemotherapy.

The position with regard to diseases of protozoal origin was different. Although the causative agents of these diseases were known, there were no methods of cultivating the micro-organisms *in vitro*. A technique for transmitting trypanosome infections through a series of mice, developed by Laveran and Mesnil (1902), enabled stable strains of trypanosomes to be maintained *in vivo*. Many protozoal infections do not easily give rise to antibody formation, and are therefore not amenable to immunological methods of treatment. However, some of the traditional remedies of medicine were fairly effective in combating certain of the protozoal infections: malaria was cured by quinine, and amoebic dysentery by emetine or ipecacuanha. Some indications of the possible effectiveness of arsenic against trypanosomes were obtained soon after the identification of these micro-organisms. Lingaard in 1899 found that arsenious acid and other inorganic arsenic preparations cured a trypanosomal disease of horses, occurring in India, known as surra; while Bruce found that arsenious acid caused a temporary remission in tsetse-fly disease in Africa.

The distribution of drugs in the animal body had received attention from other workers besides Ehrlich, and the Meyer-Overton theory, propounded in 1899, established a reasonable scientific basis for this branch of chemotherapy (Meyer, 1899; Overton, 1901, 1902). Overton showed that chemical compounds may be divided into different groups according to the rapidity with which they diffuse into cell protoplasm, the rate of diffusion generally depending on the distribution coefficient of the compound between fat and water. Anæsthetics and narcotics usually diffuse rapidly into cells, and they possess relatively high distribution coefficients. Meyer showed that in the aliphatic narcotics, strength of narcotic action was approximately proportional to distribution coefficient.

(*Development of chemotherapy by Ehrlich*

With this background, Ehrlich started on the experimental chemotherapy of trypanosome infections, largely because there was no known cure for sleeping sickness, which was becoming a major problem in the development of the continent of Africa. His first work in this field, published with Shiga in 1904, was the beginning of a systematic investigation of dyes as curative agents for trypanosomiasis in mice.) Preliminary work on the benzopurpurin series of dyes, chosen apparently because of their long persistence in mice after injection, led finally to the discovery that trypan red was both curative and prophylactic for mice infected with the disease *Mal de Caderas* (*Trypanosoma equinum*) (Ehrlich, 1907). This was the first cure of an experimentally-produced disease by administration of a synthetic organic substance of known chemical composition. Trypan red had little practical use as it was relatively ineffective against other species of trypanosomes (e.g. *T. brucei*) in mice. However, the discovery led to the introduction by Mesnil and Nicolle (1906) of two other dyes of the same series, trypan blue and afriol violet, which were effective against *T. brucei* infections in mice and cattle. Here we have the first practical result of experimental chemotherapy; trypan blue was used to cure cattle of tsetse-fly disease, and was later shown by Nuttall and Hadwen (1909 a and b) to be effective in curing piroplasmosis in dogs and cattle.

Following work on triphenylmethane dyes by Wendelstadt and Fellmer (1906), Ehrlich found that malachite green had some curative action on experimental trypanosomiasis although it was fairly toxic, especially as a prophylactic. After examination of acridine dyes and the related oxazines and selenazines, a compound with considerable trypanocidal activity and low toxicity for mice was finally produced. This was diamino-methylacridinium chloride (trypaflavin, later known as acriflavine).

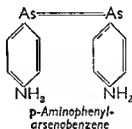
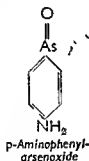
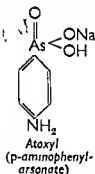
One important result of work with these dyes was the development *in vivo* of drug-resistant strains of trypanosomes.

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throughout its many stages, emphasis was continually laid on chemical combination of drugs both with the parasite and with the tissues of the host. In 1903 Ehrlich tested atoxyl against trypanosomes *in vitro*; it was without effect and he did not then test it on infected animals. Two years later, Thomas and Breinl (1905) found that atoxyl cured trypanosomiasis in mice, and trials by Koeh in Africa showed that it cured the human form of trypanosomiasis known as sleeping sickness. Although atoxyl proved to be rather toxic to humans, occasionally causing optic nerve atrophy or other severe complications, it is important as the first cure to be discovered for sleeping sickness. The successful use of atoxyl *in vivo* revived Ehrlich's interest, and he started by re-investigating its structure, which was believed at this time to be an anilido of arsenic acid. In conjunction with Bertheim, Ehrlich showed that this conception was wrong, and that atoxyl is in fact the sodium salt of *p*-aminophenylarsonic acid (Ehrlich and Bertheim, 1907).



The significance of this constitution for atoxyl was at once recognised by Ehrlich, who saw the wide possibilities opened up through preparation of homologues by substitution in the amino group. However, before he had prepared many derivatives of atoxyl, he carried out an important investigation on the mode of action of the drug, searching for the reason for the failure of atoxyl to react on trypanosomes *in vitro*. In 1909 Ehrlich and Roehl showed that reduction of atoxyl by any ordinary reducing agent produced *p*-aminophenylarsenoxide. This compound, containing arsenic in the trivalent form, had a strong *in-vitro* trypanocidal action,

In Ehrlich's laboratory, Franke and Roehl found that feeding parafochsin to mice infected with *Trypanosoma brucei* caused disappearance of trypanosomes from the peripheral blood, but, after a week or two, relapse occurred and the parasites reappeared. Administration of the drug caused them to disappear again. This process could be repeated at further relapses, but not indefinitely. After each successive administration, the time of banishment of trypanosomes from the blood became shorter, until finally the drug failed entirely to have an effect on the parasites. When trypanosomes from these mice were transferred to normal mice, they were found to be still unaffected by parafochsin, and it was evident that the parasites themselves had acquired an increased resistance to the drug. This resistance was maintained consistently through numerous animal passages.

Later work by Ehrlich showed that such trypanosomes could acquire resistance to other known trypanocidal substances such as arsenical drugs. Strains of trypanosomes were developed which were resistant to certain compounds within one chemical class, but sensitive to other trypanocidal substances. This chemical specificity suggested that chemical processes were involved in the action of drugs on parasites, and led Ehrlich to put forward his "chemo-receptor" theory of drug action. This theory is, in essence, very similar to his other side-chain theories which we have already mentioned, and accounted for the action of a drug by its combination with a specific receptor in the parasite. Resistance to a particular drug was regarded as due to reduction of affinity of a receptor for one drug without change in combining powers for other drugs. This implies that parasites possess a whole series of chemo-receptors which are specifically different from one another, and suggests that a study of resistant strains should indicate the receptor on which a drug is acting.

(*Ehrlich's work on arsenical drugs*)

The field of organic arsenical drugs saw Ehrlich's most successful contribution to medicine and to chemotherapy. This work was based on his chemoreceptor theory in so far as

Salvarsan had a striking effect in curing frambœsia (yaws), another form of human spirochætal infection. By 1913 a hospital in Surinam in Africa, in which over 300 patients with frambœsia had been constantly under treatment, had to be closed for lack of patients as one injection of salvarsan sufficed to cure the disease. Unfortunately, syphilis is not so easily cured, but, provided the disease is caught in its early stages and vigorous treatment is given, a cure can be fairly certainly effected by neoarsphenamine together with bismuth.

Ehrlich's theories of drug action

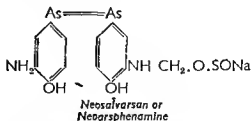
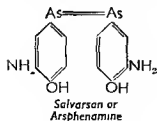
Throughout his work on chemotherapy, Ehrlich was guided by his chemo-receptor theory of drug action, together with other principles or beliefs which helped him in his selection of drugs for trial (summarised by Ehrlich, 1913). The first principle was "*Corpora non agunt nisi fixata*"; in other words, parasites were only attacked by drugs which they fixed by means of their chemo-receptors. Apparent exceptions to this principle existed, since in many cases no direct action of a drug on the parasite *in vitro* could be observed. Ehrlich explained this by supposing that the amount of drug fixed by parasites, although insufficient to kill immediately, was sufficient to prevent multiplication of parasite in the host, thus permitting phagocytic action to eliminate the infection. He showed that although spirochætes treated with salvarsan *in vitro* remained fully motile after washing free from the drug, they would not infect an animal into which they were injected. This point of view was ignored for many years, but is to-day considered to represent the most probable mode of action of most chemotherapeutic drugs which are bacteriostatic rather than bactericidal.

We should emphasise here that although Ehrlich employed a somewhat pictorial representation of reaction of drug with its receptors, his own conception of the interaction was essentially a chemical one, in which the forces involved were those of ordinary chemical reaction.

The fixing of drug by parasite Ehrlich termed a "parasitotropic" effect. Most drugs were also toxic to the host and

in contrast to the pentavalent atoxyl. Ehrlich (1909) postulated that the trypanocidal action of atoxyl *in vivo* is due to reduction of arsenic to the trivalent form by host cells. Therapeutic trials of *p*-aminophenylarsenoxide showed that it was highly toxic to both host and parasite. The arsenobenzene derivative, in which arsenic was also in the trivalent form, was found to be less toxic to animal cells, although almost as active as arsenoxido against trypanosomes.

Some evidence existed that arsenicals were also effective against spirochaetes; other workers had found that atoxyl cured fowl spirillosis, also syphilis in apes, rabbits and even humans. Atoxyl had, however, no effect against relapsing fever, a prevalent, and hitherto intractable spirochaetal disease. In view of the success of atoxyl against some spirochaetal diseases, Ehrlich was convinced that other arsenic derivatives would be found to cure relapsing fever. Turning once more to the arsenobenzene derivatives, Ehrlich and Berthelm (1912) eventually prepared the hydrochloride of dihydroxydiaminoarsenobenzene, known as salvarsan. Some idea of the scope of their work may be derived from the serial number 606 given to this compound. Salvarsan proved to be successful in curing relapsing fever both in mice and humans, and was also found by Ehrlich and Hata (1911) to cure human syphilis and trypanosomiasis.



The more soluble derivative of salvarsan introduced by Ehrlich in 1912, known as neosalvarsan or neoarsphenamine, is a condensation product of salvarsan with sodium formaldehyde sulfoxide. After careful clinical trials, Ehrlich eventually allowed it to be put on the open market as an anti-syphilitic drug. It proved to be the greatest achievement of chemotherapy up to the discovery of the sulphonamides.

spirochaetal, was reported by Morgenroth and Levy (1911). The quinine derivative, ethylhydrocuprein or "optochin," which had a powerful and specific inhibitory action on pneumococci *in vitro*, was also found to cure mice infected with pneumococci. Unfortunately, extension of the work to human cases did not show similar cures and the substance was found to be very toxic. Later work by Morgenroth showed that homologues of optochin were highly active against other bacteria *in vitro*; for example, isoamylhydrocuprein (eucupin) was strongly germicidal for diphtheria bacilli, while the iso-octyl derivative (vucin) was active against streptococci. These compounds were not active against general infections in animals, but were found to have some local antiseptic action when introduced into the site of infection. These observations of Morgenroth were the starting point for a considerable amount of work on quinine derivatives, which has not, however, resulted directly in the development of any successful chemotherapeutic agent for bacterial diseases.

During the early part of the twentieth century investigations were continued on the bactericidal action of dyes. Churchman was concerned with the selective action of gentian violet on 130 bacterial species, and divided the organisms into violet-positive and violet-negative according to whether or not their growth was inhibited by the dye (Churchman, 1912, 1913; Churchman and Michael, 1912). Simon and Wood (1914) extended their observations to a great variety of dyes and found that only basic dyes had an inhibitory action, no effect being obtained with acidic dyes. The development of strains of organisms resistant to various dyes was described by these authors and the existence of natural dye-fast strains was also noted. This was not the first case of bacterial resistance to be described, as resistance to drugs had been observed in the nineteenth century, and Morgenroth a few years previously had produced strains of pneumococcus resistant to optochin. However, the publications of Simon and Wood are interesting as they contain a theory of drug action and resistance which differs somewhat from Ehrlich's theory, and

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In arsenical drugs Ehrlich distinguished two types of groupings—the trivalent arsenic group, responsible for the toxic effect, and a "fixative" group which fixed the drug to the parasite and so allowed the toxic group to act. The fixative group was also supposed to determine the organotropic character of the drug. (In Ehrlich's opinion the aim of chemotherapy should be to achieve "*Therapia magna sterilans*," or complete recovery with one massive dose of drug. This is a very desirable aim, which has not yet been achieved by our modern chemotherapeutic drugs. Whether it will ever be attained is a matter for the future to decide.)

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Ehrlich confined most of his chemotherapeutic studies to diseases of protozoal or spirochaetal origin, and did little work on the chemotherapeutic treatment of bacterial infections, but experiments which he did carry out were of considerable theoretical importance.) In collaboration with Bechhold, he investigated the germicidal powers of substituted phenols (Bechhold and Ehrlich, 1906; Bechhold, 1909). Compounds were obtained which far exceeded all previously known phenols in their bactericidal action *in vitro* in nutritive broth, but therapeutic experiments on infected animals proved unsuccessful. This failure was shown to be due to the fact that these disinfectants combined with serum proteins to such an extent that their germicidal power was depressed.

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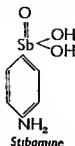
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only a local one. Both acriflavine and rivanol have since proved of value for local applications because of their low toxicity for tissues. The chemotherapy of systemic bacterial infections was, however, slow in developing, and no real advances were made in this field until the introduction of the sulphonamides in 1935.

(Protozoal and spirochaetal chemotherapy)

Following Ehrlich's discoveries, further slow progress was made in the chemotherapy of protozoal and spirochaetal infections. The trypanocidal effect of tartar emetic had been demonstrated in 1908 (Mesnil and Brimont, 1908; Plimmer and Bateman, 1908); it has proved to be of some value in the treatment of trypanocidal diseases in domestic animals and even in humans.) In 1912 Gaspar Vianna opened up the field of chemotherapy of leishmanial infections by showing that dermal leishmaniasis in Brazil could be cured by tartar emetic. This was confirmed for other leishmanial diseases in different parts of the world, and specific treatment of these diseases with antimony was soon widespread. (Kala-azar is probably the most serious and widespread of leishmanial infections; before the introduction of antimony therapy, the death-rate in India among sufferers from this disease was almost 90 per cent.)

Both sodium and potassium antimonial tartrates were found to give rise to toxic effects, and these were soon discarded in favour of the less toxic pentavalent organic preparations which are derivatives of phenylstibonic acid.



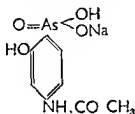
The first of these compounds to be tested was *p*-aminophenylstibonate (stibamine), the antimony analogue of atoxyl

hears a marked resemblance to some of our modern theories. They ascribed, as Ehrlich did, the inhibitory action of dyes to the existence of receptors in the micro-organism to which the dye was anchored—the receptors probably being acidic groups which reacted with the basic dyes. The receptors were considered to be “nutriceptors” responsible for carrying on the metabolism of the cell, and since they were blocked by combination with dye, the cell died, not necessarily because it had been poisoned, but because a sufficient number of its nutriceptors had been thrown out of action to bring about its starvation or inability to multiply. Adaptation to grow in the presence of inhibitory amounts of dyes was ascribed to the existence of other receptors by which the organism could carry out its nutrition and reproduction, and to the possibility of the organism “producing such receptors while the others were occupied by the dye.” No suggestion was made as to the nature of these receptors, but the remark is made that “since intracellular metabolism is intimately connected with the action of the enzymes, the question has naturally suggested itself whether the deleterious action of the dyes may not in part be referable to interference with the activity of these components.”

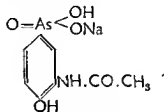
Browning and his co-workers showed that the acridine dye, acriflavine, had a strong antibacterial action which was augmented, rather than decreased, by the presence of serum; general toxicity was relatively low (Browning and Gilmour, 1913; Browning, Gulbransen and Thornton, 1917; Browning and Gulbransen, 1917). Here again Ehrlich's influence is evident; he had introduced the same compound, under the name trypanflavine, as a trypanocidal substance.

Another acridine dye, 2-ethoxy-6:9-diaminoacridine, was found by Morgenroth, Schnitzer and Rosenberg (1921) to be even less toxic than acriflavine and to possess a high bacteriostatic action. Its hydrochloride, known as rivanol, could be injected safely into humans. Morgenroth managed to cure mice of a streptococcal infection by rivanol, but only by injection immediately after infection and close to the site of application of the organism. In other words, the action was

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Orsanine



Stovarsol

arsonate, has a strong trypanocidal action, and until the discovery of amidines, has shared with tryparsamide the position of being the only satisfactory drug for the treatment of sleeping sickness in its later phases. (Stovarsol, *p*-hydroxy-*m*-acetylaminophenylarsonate, has no action on trypanosomes, but has fairly strong anti-spirochætal and amoebicidal actions, and has been occasionally used where injection is impracticable, as it can be administered orally.) Fourneau's work is also of considerable theoretical interest, as it illustrates well the high specificity of drug action.

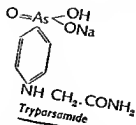
(Hitherto, synthetic chemotherapy had been chiefly concerned with organo-metallic trypanocidal and anti-spirochætal drugs. The introduction in 1920 of Bayer 205 (Germanin or Moranyl) marked an important departure from this field. The constitution of the drug, synthesised by the German firm of Bayer, was originally withheld; but a fine piece of work by Fourneau (1924), involving the synthesis of many ureas of the acynaphthylamine-sulphonic acid type, led to a compound (Fourneau 309) with the same therapeutic properties as Bayer 205. Fourneau found that the chemical specificity of his compound was most marked; the slightest change in structure resulted in a diminution of trypanocidal activity.

THE BASIS OF CHEMOTHERAPY

(Uhlenhuth, Mulzer and Hügel, 1913); it proved to be too unstable in solution and too uncertain in action to be used therapeutically. Its acetyl derivative, stibenyl, was successfully employed by Caronia in 1916 for the treatment of kala-azar in Italy, but it has been found to be ineffective in India.

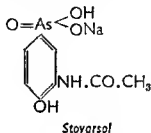
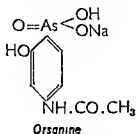
After this, slow but steady advance was made in the chemotherapy of diseases of spirochaetal and protozoal origin. Bismuth was introduced for the treatment of syphilis by Sazerac and Levaditi (1921). They showed the therapeutic activity of sodium potassium tartrobismuthate in rabbit syphilis and in some human cases. Actually, the use of bismuth in syphilis was first suggested by Balzar (1889), but it does not appear to have been tried out; it was found to be curative in fowl spirochaetosis by Robert and Sauton (1916) but its value again passed unnoticed until 1921. Since then, more than 200 new bismuth compounds have been produced, often with little or no preliminary study to determine whether they were an improvement on already known compounds. The action of organo-bismuth compounds appears to be due to the liberation of metallic bismuth, and the value of different preparations seems to depend on their power of penetrating the parasite cell.

Jacobs and Heidelberger (1919), in attempting to find a satisfactory trypanocidal compound, prepared a large number of organic arsenical compounds, and from these selected sodium N-phenylglycineamide-p-arsenate, now known as



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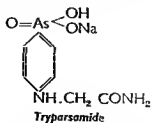
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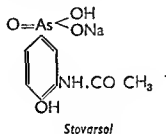
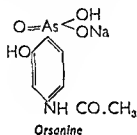
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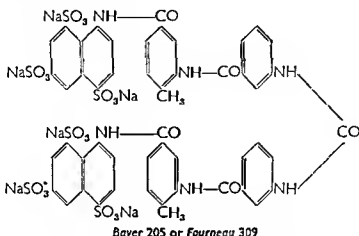
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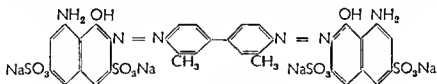
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He therefore concluded that his substance had the same structure as Bayer 205.



The drug is said to have been produced by Bayer in a search for a colourless substance related to the trypanocidal dyes, trypan blue and afridol violet, which were introduced in 1906 by Mesnil and Nicolle. Trypan blue was used for the treatment of trypanosomiasis in cattle, but, since bright blue meat was unsaleable, the Bayer company attempted to find a colourless trypanocide. Afridol violet already contained

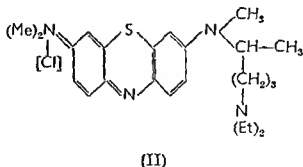
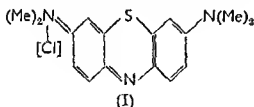


one urea linkage; the further use of amide linkages instead of azo groups provided a colourless substance.

(Bayer 205 has proved to be an extraordinarily useful trypanocidal agent; its chemotherapeutic index for mice is about 300, the highest for any compound known at that time.

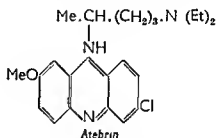
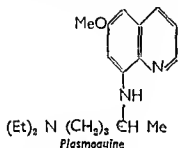
It is interesting to note that Ehrlich (1913) considered a therapeutic index of 10 or even 5 was as high as could be expected. One disadvantage of the drug is that it is unable to cure sleeping sickness in the advanced stages when trypanosomes have attacked the brain, since it cannot pass into the *cerebrospinal fluid*. However, provided that it is given in the first few weeks after the beginning of the illness, there is a reasonable chance of cure. Later stages of the disease must still be treated with either tryparsamide or orsanine, both of which penetrate to the cerebrospinal fluid. A useful feature of Bayer 205 is its persistence in action, probably due to its slow rate of excretion. When administered prophylactically, a single dose may confer immunity to sleeping sickness for several months.

Other successful investigations originating from the work of Ehrlich were in the antimalarial field. It will be remembered that Ehrlich in 1891 found that methylene blue (I) had some curative effect on malaria.) The Bayer research chemists accordingly tried the effect of replacing the methyl groups attached to the aromatic amino groups of methylene blue



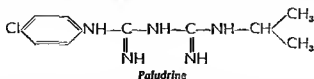
with other alkyl groups. Next they tried replacing the methyl groups with basic alkyl groups, producing compound (II) (see formulæ) with the favourable chemotherapeutic index of 8.

(The work on methylene blue did not produce a compound of any practical value, but it indicated some relationship between antimalarial effect and chemical structure. The experience gained was applied to other ring systems, with the result that plasmoquine, a derivative of 6-methoxy-8-aminoquinoline with a therapeutic index of 30, was produced in 1924 (Schulemann, Schönhöffer and Wingler, 1932). Success in the quinoline



series naturally led to an examination of similar substitutions in other heterocyclic nuclei, and led eventually to the acridine derivative known as atebrin or mepacrine (Mauss and Mietzsch, 1933). This substance is very effective against human malaria, both prophylactically and curatively, and has a low toxicity. It proved to be superior to quinine during the war of 1939-45, when it was shown by field trials to be a prophylactic against benign and malignant tertiary malarias and a cure for the malignant tertiary form.

(Atebrin has now been supplemented by paludrine, an anti-malarial drug synthesised by chemists of Imperial Chemical Industries of Great Britain in 1944 (Curd and Rose, 1946).)



Paludrine is a biguanidine compound, the result of a search for antimalarial drugs among pyrimidine derivatives. The pyrimidines were found to have antimalarial properties if they possessed configurations which permitted certain tautomeric changes. Working on the theory that this tautomeric capacity conferred antimalarial activity, the pyrimidine ring was found

to be unnecessary, and biguanidine derivatives with high activity were produced.

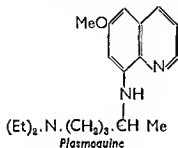
(Paludrine is proving to be a most potent and non-toxic antimalarial drug. It is active against all three forms of malaria, and possesses the property, absent from other anti-malarial drugs, of preventing the development of parasites in the pre-erythrocyte stage following primary infection (Fairley, 1946).)

(*Pharmacological basis of chemotherapy*)

The successful development of chemotherapy, as we have described it, appears at first sight to be a purely empirical process based upon patient trial of innumerable analogues of a compound of known activity. This is not strictly true; since 1920 there has gradually developed a pharmacological basis for chemotherapy concerned with the action, distribution and excretion of chemotherapeutic drugs in the body. Much of the pioneer work on this subject was carried out by Voegtlin between 1921 and 1930 (Voegtlin, 1925). He emphasised the importance of this side of chemotherapy since it determined to a great extent whether or not a drug which was active *in vitro* would be similarly active *in vivo*. He showed that parasitidal action *in vivo* is dependent not only on the toxicity of drug for the parasite, but also on the rate of excretion of drug and its power of penetrating tissues. He attempted to explain the differential action of drugs in poisoning parasites rather than the host, a fact simply accepted by Ehrlich. Voegtlin suggested that either the capacity of host cells to convert the toxic form of a drug into a non-toxic form was greater than that of parasites, or that parasites had a greater permeability for the drug than the host cells.

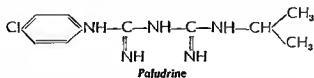
Voegtlin provided the first practical demonstration of Ehrlich's theory that the pentavalent form of an arsenical drug is converted by the host into the active trivalent oxide form; he also established the point that arsenobenzene derivatives are not active as such but are transformed in the host to the active arsenoxide form. This point seems to

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have escaped Ehrlich in his development of salvarsan (Voegtlin, Dyer and Leonard, 1923). When salvarsan or other arsenohydrobenzene derivative was injected into a rat infected with trypanosomes there was a latent period of several hours before destruction of the parasite, but the trivalent oxide form of salvarsan had an immediate trypanocidal action. The toxic effect of arsenoxides was shown to be due to their action on sulphydryl groups in the host tissues, since glutathione, a sulphydryl-containing peptide, protected an animal when injected immediately after a lethal dose of arsenoxide. Glutathione and various other organic sulphydryl compounds were also found to protect trypanosomes both *in vitro* and *in vivo* from the lethal effect of arsenoxides. A direct practical result of this work of Voegtlin was the introduction, as a therapeutic drug, of the arsenoxide derivative of salvarsan, under the name mapharsen (*m*-amino-*p*-hydroxyphenyl-arsenoxide). As with other arsenoxides, toxicity is high, a fact which caused Ehrlich to discard the compound as a practical drug; nevertheless, because of its potent action on parasites, mapharsen possesses a favourable therapeutic index.

(Voegtlin's ideas do not appear to have taken root, for much speculation continued for some years on the nature of chemotherapeutic action. Did drugs act directly on the parasite, or did they act indirectly through the host, either by stimulating the defence mechanism, or by giving rise to the production by the host of a parasitocidal substance? The main reason for the persisting doubt appears to have been the absence of correlation between *in-vivo* and *in-vitro* action of drugs. Some drugs appeared to have no direct killing action *in vitro*, but undoubtedly countered the organisms *in vivo*. Equally puzzling was the *in-vitro* action of emetine and cephaeline, the chief alkaloids of ipecacuanha, known to be effective cures for amoebic dysentery. Dale and Dobell (1917) found that these alkaloids were less toxic to isolated dysentery amoebae than other alkaloids which were not curative for the disease. This lack of correlation between *in-vitro* and *in-vivo* observations was a direct result of inability to culture or

even maintain the organisms in question outside the animal body.) The time of survival of trypanosomes or dysentery amoebae in the media used at that time was a matter of a few hours, and it is obvious that no extended observations were possible on parasitic reactions to drugs. Similarly, the effects of drugs on growth and reproduction could not be determined, and the theory originally propounded by Ehrlich, suggesting that drugs acted by preventing multiplication, was discarded for want of positive evidence (review by Dale, 1923).

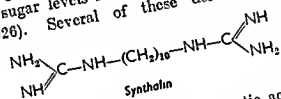
The introduction of a culture medium for dysentery amoebae by Bocck and Drbohlav (1925) enabled Dobell and Laidlaw (1926) to show that emetine and cephaeline were far more poisonous than other alkaloids under suitable cultural conditions, and that very dilute solutions, although not immediately toxic, were lethal to the organisms. The concentration required to kill immediately bore no relation to the minimal concentration which was lethal if maintained for a period of days. These observations accounted for the anomalous results of Dale and Dobell. Later Laidlaw, Dobell and Bishop (1928) were able to cultivate the organisms in a purely liquid medium, in which a concentration of emetine of 1 in 5,000,000 was sufficient to inhibit growth.

The problem of *in-vitro* cultivation of trypanosomes has not yet been completely solved, but Yorko, Adams and Murgatroyd (1929) developed a medium which would maintain trypanosomes alive and motile for twenty-four hours. This opened up the field of trypanosome therapeutics considerably and has led to a better understanding of drug action in these organisms. At the same time, these workers found that trypanosomes consume enormous amounts of glucose *in vitro*—400 million trypanosomes (representing about 27 mg. of material) causing between 2.0 and 2.5 mg. of sugar to disappear in 1 hour at 37° C. This fact, fully confirmed by later work, led directly to the important discovery of the amidine group of drugs. In discussion of the *in-vitro* cultivation of trypanosomes it must be emphasised that the difficulty lies, not in the subculture of viable protozoa, but in the

maintenance of pathogenic strains in the form in which they exist in the animal host (cf. Weinman, 1946; Brand, Johnson and Rees, 1946).

Amidines

Jancsó and Jancsó (1935b) concluded that the trypanocidal action of Bayer 205 was due to its interference with the carbohydrate metabolism of trypanosomes, as the drug produced changes in trypanosomes similar to those resulting from removal of sugar from the medium in which the parasites were suspended. In view of the high carbohydrate metabolism of trypanosomes, they decided to examine the reaction of parasites to guanidino derivatives, which were known to lower blood sugar levels in animals (Frank, Northmann and Wagner, 1926). Several of these derivatives (especially

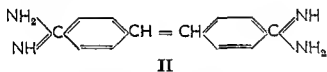
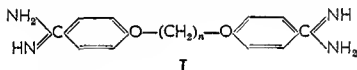


synthalin) were found to exert a therapeutic action on mice infected with *Trypanosoma brucei*. The Jancsós concluded that the therapeutic effect was an indirect one, due to continuous hypoglycemia depriving the trypanosomes of the necessary glucose for their development. Schern and Artagaveytia-Allende (1936) showed independently the therapeutic action of synthalin in rats infected with trypanosomes.

Lowrie and Yorke (1937) considered it improbable that a degree of hypoglycemia compatible with life of the host would be sufficient to affect the parasite adversely, so they examined the *in-vitro* effect of synthalin on trypanosomes. This was found to be extremely powerful, a concentration of 1 in 200 millions having a pronounced trypanocidal action. However, insulin had no effect on trypanosomes either *in vitro* or *in vivo*, while synthalin produced little hypoglycemia in the normal animal unless given in doses so large as to cause liver damage. They therefore concluded that synthalin exerted a direct toxic effect on trypanosomes.

To test this theory, a large number of guanidines, isothioureas, amidines and amines, with alkyl and alkylene chains, were prepared and examined for trypanocidal activity (King, Lourie and Yorke, 1938). Certain of the diamidines showed a powerful trypanocidal action both *in vitro* and *in vivo*; the most active compound, undecane-diamidino, producing almost 100 per cent. cures in mice and rabbits infected with *T. rhodesiense*.

The firm of May and Baker later produced a series of aromatic derivatives containing the amidine group. Some of these have proved to be valuable chemotherapeutic drugs (Ashley, Barber, Ewins, Newbery and Self, 1942). The 4:4-diamidinodiphenoxyalkanes (I where $n = 3$ or 5) showed low toxicities, 4:4-diamidinodiphenoxypentane having a therapeutic index of 15. 4:4-Diamidinostilbene (II) was even less toxic with a therapeutic index of 30.



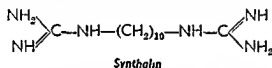
(The amidines are fairly unspecific in their action on protozoa, and have been shown to have a therapeutic action in trypanosomiasis, leishmanial infections such as kala-azar, piroplasmiasis such as *Babesia canis*, and malaria infections of birds and monkeys. 4:4-Diamidinostilbene acts effectively against the early stages of sleeping sickness, but, like Bayer 205, is unable to penetrate into the cerebrospinal fluid, and is thus of little value in the later stages. It is very effective against kala-azar, but, although it has an antimalarial action, it is of little use in treating human malaria. The amidines have no action against spirochaetes.)

Treatment of trypanosome infections in cattle has been extended by the discovery that certain phenanthridines are curative against infections caused by *Trypanosoma congolense*

maintenance of pathogenic strains in the form in which they exist in the animal host (*cf.* Weinman, 1946; Brand, Johnson and Rees, 1946).

Amidines

Jancsó and Jancsó (1935b) concluded that the trypanocidal action of Bayer 205 was due to its interference with the carbohydrate metabolism of trypanosomes, as the drug produced changes in trypanosomes similar to those resulting from removal of sugar from the medium in which the parasites were suspended. In view of the high carbohydrate metabolism of trypanosomes, they decided to examine the reaction of parasites to guanidine derivatives, which were known to lower blood sugar levels in animals (Frank, Northmann and Wagner, 1926). Several of these derivatives (especially



synthalin) were found to exert a therapeutic action on mice infected with *Trypanosoma brucei*. The Jancsós concluded that the therapeutic effect was an indirect one, due to continuous hypoglycæmia depriving the trypanosomes of the necessary glucose for their development. Schern and Artagaveytia-Allende (1936) showed independently the therapeutic action of synthalin in rats infected with trypanosomes.

Lourie and Yorke (1937) considered it improbable that a degree of hypoglycæmia compatible with life of the host would be sufficient to affect the parasite adversely, so they examined the *in-vitro* effect of synthalin on trypanosomes. This was found to be extremely powerful, a concentration of 1 in 200 millions having a pronounced trypanocidal action. However, insulin had no effect on trypanosomes either *in vitro* or *in vivo*, while synthalin produced little hypoglycæmia in the normal animal unless given in doses so large as to cause liver damage. They therefore concluded that synthalin exerted a direct toxic effect on trypanosomes.

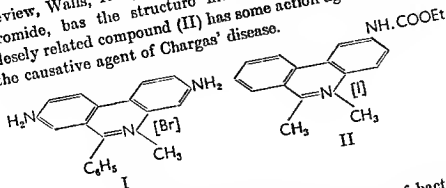
fatal hæmolytic streptococcal infections in mice, cured chronic streptococcal infections in mice, and favourably influenced staphylococcal infections in rabbits, but had no effect on pneumococcal or other experimental infections and was without action *in vitro* on bacteria. This work was not published till 1935 (Domagk), but various reports of clinical trials of the substance in 1934 showed that it cured erysipelas and streptococcal empyema. Clinical trials reported in 1935 established that prontosil is highly effective against most hæmolytic streptococcal infections, particularly puerperal fever. A chemotherapeutic agent for bacterial infections had been found.

The development of prontosil can be traced back to work on azo dyes. In 1909, Harlein of I.G., working on textile dyes, synthesised azo dyes with sulphonamide and substituted sulphonamide groups. These dyes were characterised by the stable complexes which they formed with wool proteins. Later, Eisenberg (1913) found that the dye chrysoidin (2:4-diaminoazobenzene) was bactericidal *in vitro* but had little effect in the living animal. In an attempt to increase the bactericidal properties of quinine derivatives, dyes based on hydrocupreine were prepared by Heidelberger and Jacobs (1919); one of these was *p*-aminobenzenesulphonamido hydrocupreine. The authors commented on the high bactericidal potency of these compounds but published no further experimental work on the subject. Work by Mietzsch and Klarer of I.G. on azo compounds led to the development of compounds of greatly increased bactericidal power when compared with known compounds, but they had no effect *in vivo*. However, Domagk observed that azo compounds containing sulphonamide had slight activity in combating streptococcal sepsis in mice. This observation directed further work into the channels eventually leading to prontosil.

After the publication by I.G. of their results in 1935, Levaditi and Vaisman (1935) in France confirmed the results on mice with a preparation of prontosil prepared for them by Girard and called "rubiazol." Soon came the suggestion by Tréfouël, Tréfouël, Nitti and Bovet (1935) that prontosil was broken in the host tissues at the azo linkage yielding

THE BASIS OF CHEMOTHERAPY

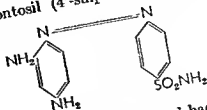
(review, Walls, 1947). The most useful compound, dimidium bromide, has the structure indicated below (I). Another closely related compound (II) has some action against *T. cruzi*, the causative agent of Chagas' disease.



Development of Sulphonamides

In the early 'thirties, as far as the treatment of bacterial infections was concerned, little of value had come out of chemotherapy. In 1930 the view was being expressed that bacteria were not susceptible to destruction by drugs in the host, possibly because their metabolism was so similar to that of host cells that anything capable of toxic action against bacteria was sure to be equally toxic to the host tissues. Serological treatment was considered to be the only method of combating bacterial infections and a considerable amount of research was done in this field. The introduction of prontosil in 1935 changed the situation, and it was soon realised that a new era in bacterial chemotherapy had opened.

The use of a drug called "streptozon" on a ten-month-old infant dying of staphylococcal septicæmia was reported by Foerster (1933) to have produced a dramatic cure. Streptozon was produced by the firm of I.G. and was the compound later known as prontosil (4'-sulphonamido-2:4-diaminoazo-



benzene). Patent cover for this compound had been obtained in 1932. Domagk of I.G. at that time observed that, when given by mouth, prontosil prevented the evolution of otherwise

the development of a new type of chemotherapeutic agent in the antibiotics. These are soluble antibacterial substances produced by micro-organisms during growth on suitable media.)

(Since the beginning of bacteriology, inhibition of growth of one bacterial species by the presence of another micro-organism was an established fact, and its possible application to the field of therapeutics was realised.) Pasteur and Joubert (1877) noted the antagonistic effect of aerobic bacteria on the growth of *Bacillus anthracis*, and even found that death of animals from anthrax could sometimes be prevented by including some of these aerobic bacteria in the infective dose of *B. anthracis*. Pasteur ascribed the effect to the consumption of oxygen by the aerobic organisms, but Babès (1885) interpreted experiments on growth inhibition of one organism by another as due to a chemical substance produced by the antagonistic organism. Emmerich and Low (1899) prepared an extract of *Pseudomonas pyocyanea* to which they gave the name pyocyanase. Highly diluted pyocyanase was found to have a destructive effect against pathogenic cocci, and against diphtheria, cholera, typhoid and plague organisms. These authors suggested that pyocyanase might be of use clinically, but it proved too toxic except for local application. Attempts to use pyocyanase clinically were continued for about twenty years but it gradually fell into disrepute as a remedy, possibly owing to the loss or degeneration of the original antibiotic-producing strain. There is no doubt that *Pseudomonas pyocyanea* can produce substances which are highly bacteriostatic, though it remains to be seen whether they have any clinical application (Hays *et al.*, 1945). Bacteriolytic substances have also been obtained from bacteria and tested therapeutically. Nicolle (1907) isolated from *Bacillus subtilis* a thermostable substance with lytic action against many pathogenic organisms. A considerable amount of work was subsequently carried out on these bacterial lysins in the hope that they could be used therapeutically, but they have proved toxic to animals. However, Gratia and Dath (1924, 1925, 1926) extracted a lytic agent from streptothrix mould which

p-aminobenzenesulphonamide, which was the therapeutically active principle. The basis for this suggestion was the fact that diazotised benzenesulphonamide derivatives quite different from prontosil still possessed anti-streptococcal properties, while derivatives in which *p*-aminobenzenesulphonamide was replaced by other groups were inactive.

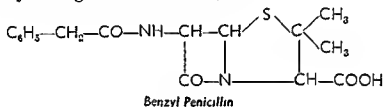
No great attention was paid in the medical literature to these important advances until the appearance of two English papers in 1936. Colebrook and Kenny (1936) showed that although prontosil was inactive in the test tube, it did produce an increase in the bacteriostatic power of the blood of patients. They also established the value of prontosil therapy in puerperal sepsis. Buttle, Gray and Stephenson (1936) confirmed the French findings that *p*-aminobenzenesulphonamide (sulphanilamide) had a curative effect on streptococcal infections in mice, and showed that it was also of value against meningococcal infections. The French workers later showed that sulphanilamide exerted a bacteriostatic effect on susceptible organisms *in vitro*, without being immediately lethal. The *o*- and *m*-aminobenzenesulphonamides and *p*-acetyl sulphanilamide were without sulphanilamide effect (Nitti, Bovet and Depierre, 1937). Finally, Fuller (1937) confirmed the suggestion of Tréfouël and co-workers that prontosil was split in the host to *p*-aminobenzenesulphonamide.

Many other sulphonamide derivatives have been prepared and found to be more active than sulphanilamide and to combat a wider range of infections. The first really effective one was sulphapyridine or "M and B 693," prepared by May and Baker Ltd., and tested by Whitby (1938). It was shown to be particularly effective against pneumococcal infections. Research in the sulphonamide field still continues to-day, and is opening up ever-wider aspects in chemotherapy as more active and less toxic drugs are found, with a greater range of action over different bacterial types.

(Antibiotics

The sulphonamides were the first class of drug to be used clinically against bacterial infections. Lately we have seen

Heatley, Jennings, Orr-Ewing and Sanders, 1940; Abraham, Chain, Fletcher, Florey, Gardner, Heatley and Jennings, 1941). The material was effective *in vivo*, subcutaneous injections producing 100 per cent. cures of mice infected with *Strep. hæmolyticus*, *Staph. aureus* or *Clostridium septicum*. Florey and his school have continued to carry out chemical, bacteriological and pharmacological work on penicillin, with the result that it is now produced on a vast scale for the treatment of many bacterial infections. The chemistry of penicillin has been worked out in many laboratories; several forms of the substance are known, one of which, benzyl penicillin (penicillin G), has the following constitution (see review by du Vigneaud *et al.*, 1946).



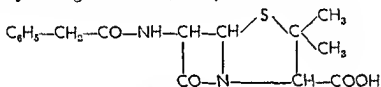
Penicillin is bacteriostatic to most Gram-positive organisms, and also to spirochaetes; it has little or no action against Gram-negative organisms. It is highly active, being bacteriostatic in dilutions greater than 1 in 10^8 , and is completely non-toxic. Its activity is not affected by tissue proteins or breakdown products, or pus, and is relatively unaffected by the number of bacteria present. In these respects it is an ideal chemotherapeutic agent. It is, however, very rapidly excreted in the urine, and cannot be taken by mouth as it is destroyed by acid. It must therefore be administered in large and frequent doses by injection or intravenous drip. Other disadvantages of penicillin are its extreme lability, low yields and high cost of production. These disadvantages are all outweighed by its low toxicity and wide range of application, with the result that penicillin has widened the field of bacterial chemotherapy to an extent which would have been unbelievable fifteen years ago. (The synthesis of penicillin has proved to be very difficult, with yields of the order of 0.2 per cent. However, when full investigations have been

had been grown on dead *Staph. aureus*, and this substance was employed, together with a bacteriophage, in the successful treatment of *Staph. aureus* carbuncles.

Many fungi have been found to produce substances with antibacterial action. Gosio (1896) produced from a *Penicillium* a crystalline substance which inhibited the growth of anthrax bacilli. He was unable to carry out tests on animals owing to lack of material, but the substance has since been re-isolated under the name mycophenolic acid and found to be useless as a chemotherapeutic agent although active *in vitro* (Florey, Gilliver, Jennings and Sanders, 1946). Filtrates from *Aspergillus fumigatus* were found by Vaudremer (1913) to cause attenuation of *Mycobacterium tuberculosis*, and were used to treat human tuberculosis, apparently with some success. Recent work has shown that this mould produces four antibiotic substances, one of which, helvolic acid, has some action against the tubercle bacillus *in vitro* (Chain, Florey, Jennings and Williams, 1943; Jennings, 1945).

(In 1929 Fleming observed that on certain agar plates in which *Staph. aureus* was contaminated by a mould, the staphylococcus colonies were transparent and undergoing lysis. He identified the mould as a *Penicillium* and found that broth in which it had been grown had bactericidal and bacteriolytic properties against pyogenic cocci and the diphtheria group of bacilli, but was inactive against Gram-negative organisms such as *Haemophilus influenzae*, *Escherichia coli* or *Eberthella typhosa*.) The name penicillin was given to active filtrates of the broth.) Fleming showed that it was almost completely non-toxic to animals, to humans, and to leucocytes, and therefore suggested that it would be a useful antiseptic for infected wounds. Subsequent attempts by Clutterbuck, Lovell and Raistrick (1932) to concentrate the active principle proved unsuccessful because of its instability and low concentration in culture filtrates. These authors showed, however, that the mould could be grown on a synthetic liquid medium. Eventually there was isolated from the culture medium of *P. notatum* a water-soluble powder with remarkable antibacterial activity (Chain, Florey, Gardner,

Heatley, Jennings, Orr-Ewing and Sanders, 1940; Abraham, Chain, Fletcher, Florey, Gardner, Heatley and Jennings, 1941). The material was effective *in vivo*, subcutaneous injections producing 100 per cent. cures of mice infected with *Strep. haemolyticus*, *Staph. aureus* or *Clostridium septicum*. Florey and his school have continued to carry out chemical, bacteriological and pharmacological work on penicillin, with the result that it is now produced on a vast scale for the treatment of many bacterial infections. The chemistry of penicillin has been worked out in many laboratories; several forms of the substance are known, one of which, benzyl penicillin (penicillin G), has the following constitution (see review by du Vigneaud *et al.*, 1946).



Benzyl Penicillin

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carried out on the groups essential for activity, it is to be hoped that derivatives will be synthesised with all the advantages of penicillin, but with few of its disadvantages.)

(The isolation by Dubos and Hotchkiss (1941) of the two antibacterial substances gramicidin and tyrocidine from *Bacillus brevis* was the result of rational attempts to produce antibacterial substances.) Dubos started by attempting to find a microbial enzyme able to attack the Gram-positive substance in pyogenic cocci. This was done by serial subculture of soil organisms in a medium containing large amounts of living organisms. An organism (*B. brevis*) capable of using coccal protein as a source of food was thus selected (Dubos, 1939). Bacteriostatic substances were found in the growing culture, and were shown to be more or less stable alcohol-soluble toxins which the organisms released on autolysis (Dubos and Cattaneo, 1939). From the alcohol extract, the antibacterial substances gramicidin and tyrocidine were isolated by crystallisation. These are both polypeptides of molecular weight 3000 or less, containing relatively large amounts of *d*-amino acids (gramicidin contains 50 per cent. of *d*-amino acids) (Hotchkiss, 1944). Tyrocidine has many basic groups and shows antibacterial properties similar to those of the cationic detergents, i.e. combining with or precipitating protein generally; it is therefore of little use therapeutically. Gramicidin has no excess of free acidic or basic groups, and is somewhat less toxic; also, it is bacteriostatic rather than directly lethal. It is only of use clinically when applied at the site of infection as it is too toxic for general use. Recently, Russian workers have reported the isolation of another antibiotic polypeptide, gramicidin-S (Belozersky and Passhina, 1944). It is believed to be a cyclic deca-peptide, with the following arrangement of amino acids: *l*-valine, *l*-ornithine, *l*-leucine, *d*-phenylalanine, *l*-proline (Consden, Gordon, Martin and Synge, 1947).

An antibiotic substance known as streptomycin has been isolated from an *Actinomycete* by Schatz, Bugie and Waksman (1944). It is highly active against some organisms not attacked by penicillin, such as *Mycobacterium tuberculosis* and the Gram-negative *Escherichia coli* and *Pseudomonas*

pyocyanea. Its therapeutic value against tuberculosis is at present under investigation.

The subject of antibiotics is very much in its infancy. Isolations and trials of new substances obtained from micro-organisms are continually being reported. The chemistry of antibiotics is a large field in itself, and should yield much valuable material for future building stones of the science of chemotherapy (review, Benedict and Langlykke, 1947).

CHAPTER II

CELL METABOLISM

THE early successes achieved by chemotherapy tended to obscure the empirical nature of the researches leading to these results. The chief reason for this empiricism was that, until comparatively recently, research was concerned mainly with the action of drugs when injected into infected animals. This method, while it gave satisfactory practical results, involved such a host of unknown variables that no real advance in knowledge of the mode of action of drugs was possible.

For chemotherapy to grow as a science, attention must be devoted to the fundamental aspects of drug action. Drug distribution in the host must be understood; the permeability of cells to drugs and the effects of drugs on cell permeability must be elucidated; the altered metabolism and reproduction of pathogen in the presence of drug must be interpreted in terms of cellular biochemistry. All these problems and more constitute the foundations for a science of chemotherapy; at the present time we are only beginning to probe their nature. We are in the position of an aeroplane pilot flying above a fog bank, able to see some imposing peaks, but unable to do more than guess at the nature of the foundations of those peaks, or to find a way through the fog to a secure base. Our best approach to the foundation is to obtain as clear a picture as possible of the enzymic make-up of living cells, so that, eventually, we can reconstruct in exact chemical terms the series of events, which we call cell metabolism, by which life is carried on. The knowledge so gained should enable us to see through the fog hiding the foundation of our science, to appreciate the action of drugs on cell metabolism, and so to gain a secure base from which to conduct future operations in our search for chemotherapeutic substances.

Drugs as enzyme inhibitors

During the last twenty years considerable progress has been made in tracing a rough outline of cellular metabolism ; this progress has depended to a large extent on improved techniques which permit the isolation of pure enzymes. Even before the end of the nineteenth century, however, investigation of the crudest enzyme preparations had led to the recognition of the fundamental role of these biocatalysts in the living cell.

Preliminary work on enzymes, carried out between 1830 and 1840, is associated with the great names of chemistry such as Liebig, Wohler, and Berzelius. Enzymes were then pictured as catalysts similar in action to inorganic catalysts, and any suggestion that enzymes were necessarily associated with life was strenuously opposed. The correct conclusions were only reached after much heated discussion, mostly based on yeast fermentation, between the chemists, led by Liebig, and the biologists, led by Pasteur. Liebig held that yeast was a catalyst formed by the action of atmospheric oxygen on non-living nitrogenous matter in fermentable liquids. Pasteur (1860) concluded that : " the chemical act of fermentation is essentially a phenomenon correlative with a vital act, commencing and ceasing with the latter. I am of the opinion that alcoholic fermentation never occurs without simultaneous organisation, development and multiplication of cells or the continued life of cells already formed. The results expressed in this memoir seem to be completely opposed to the opinions of Liebig and Berzelius. If I am asked in what consists the chemical act whereby the sugar is decomposed and what is the real cause, I admit that I am completely ignorant of it."

During the same year (1860) Berthelot showed that by maceration and washing of yeast, a cell-free preparation could be obtained which inverted cane sugar in the same way as did live yeast. The active principle could be precipitated by alcohol, washed and redissolved without loss of activity. He accordingly suggested that yeast acted on sugar by means of ferments which it was able to secrete. It is clear, he remarks, that the living cell itself is not the ferment but the producer of it.

Thereafter, more and more enzymes were identified and their activities correlated with those of the living cell. Finally, in the last quarter of the nineteenth century, we find that the enzymic nature of microbial action is fairly well established. Thus in 1899, Duclaux in his text book *Traité de Microbiologie*, when discussing the analogy between enzymes and microbes, says: "What one can do, the others can also, and the apparent strangeness of this identity of action between something living and something lifeless disappears partly when one learns that everything which we call the vital manifestation of a microbe occurs through the intermediation of an enzyme, which can be extracted and function outside of it. . . . Thus we can extract from it a substance which respire for the cell, another which digests its food, etc." Duclaux also reaches the interesting conclusion that the microbial cell does not differ essentially from "higher animals."

A logical sequence to the idea that enzymes are associated with microbial action is the investigation of the effect of antiseptics and drugs on enzymes. We find work on this subject as early as 1875, when Nasse investigated the effect of quinine, caffeine, strychnine and other alkaloids on yeast invertase, saliva and the pancreatic ferment; he found considerable inhibition of invertase by quinine and strychnine. Hüfner (1874), wanting to find a means of preventing the development of micro-organisms in animal fluids without destroying soluble ferments, remarked that almost all substances capable of killing lower organisms destroy or inhibit the action of these ferments. Thereafter, a considerable amount of work was done on the inhibition of enzymes by antiseptics, although the results were unreliable, as the effect of pH on enzyme action was not then appreciated. Comparisons were made between the action of antiseptics on certain types of cell-free enzymes and on similar enzymes acting in the live bacterial cell; thus, Fermi (1892) compared the action of thymol on trypsin and proteolytic bacteria. Duclaux (1899) realised that not all antiseptics act adversely on all enzymes, while some enzyme poisons do not act as antiseptics. Buchner, Buchner and Hahn (1903) noted that the inhibitory effect of antiseptics

on the fermentative powers of yeast juice was considerably less than their effect on fermentation by living cells.

After 1900, investigations gradually began to assume a more quantitative aspect. Hata (1909) investigated the effect of mercuric chloride, a powerful antiseptic, and showed that it inhibited many proteolytic enzymes but that inhibition could be reversed by substances, such as K_2S , which precipitate the mercury radical. This important observation on the reversible inactivation of enzymes by mercuric chloride is comparable with a much earlier observation that the disinfectant action of mercuric chloride could be antagonised by ammonium sulphido (Geppert, 1889).

Ehrlich, as a result of his early work on vital staining, was one of the first to stress that in cells there exist substances capable of oxidation and reduction which regulated the oxygen content of the cells. He termed these substances "chemo-receptors," but unfortunately appeared to ignore their relation to enzymes. However, by providing a theory of drug action based on direct chemical combination of drug with parasite, he stimulated the *in-vitro* study of the action of drugs on cells. Ehrlich's speculations were extended by Simon and Wood (1914) in the following terms: "Since intracellular metabolism is intimately connected with the action of enzymes, the question has naturally suggested itself whether the deleterious action of the dyes may not in part be referable to interference with the activity of these components." They suggest that the basic groups of inhibitory dyestuffs combine with acidic groups of "nutriceptors" of micro-organisms, and so inhibit the normal function of the "nutriceptors," which is to anchor and split foodstuffs. The cell dies, not necessarily because it has been poisoned, but because a sufficient number of nutriceptors have been thrown out of action to bring about its starvation or inability to multiply.

The suggestions of Ehrlich and of Simon and Wood were purely speculative, but they were soon given an experimental basis by Jacoby (1916) in a further study of the action of mercuric chloride. Jacoby found that the enzyme urease, which had been isolated from jack-bean and catalysed the

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was suggested by some important work of Voegtlin, Dyer and Leonard (1923). The toxic effect on animals of the arsenoxido group was prevented by simultaneous injection of glutathione, a naturally-occurring polypeptide containing a free sulphydryl group. On the basis of the known chemical combination of arsenic with sulphydryl groups, the suggestion was made that arsenical drugs combine with sulphydryl groups in the cell, and inhibit essential metabolic processes associated with these groups. An excess of glutathione in the blood, or even of other sulphydryl-containing compounds such as thioglycols, can protect the essential cellular sulphydryl compounds. It is interesting to note that Ehrlich (1909) also suggested, but without experimental foundation, that sulphydryl groups could act as "chemo-receptors" for metals.

Investigations from 1913 until 1929 by Warburg and by Keilin included studies on the effect of poisons and narcotics on the respiration of intact organisms, and provided a much-needed link between isolated enzymes and cellular metabolism. In living intact cells, inhibition of respiration by a homologous series of narcotics, such as the urothanes or aliphatic alcohols, was found by Warburg (1914) to increase with increase in chain length, following lipid/water distribution coefficients. When the same narcotics were added to cell-free enzyme preparations the homologous series rule also applied, but inhibition was less than in the intact cell; Warburg suggested that this was due, at least in part, to the selective action of the cell membrane which transmitted lipid-soluble substances rapidly to the interior of the cell. Certain lipid-insoluble substances, such as barium chloride, had no inhibitory effect on intact cells, but acted as powerful poisons after damage of the cell wall. Cyanide, although it has an oil/water distribution coefficient of only 0.1, inhibited respiration at far lower concentration than narcotics and had a highly specific effect in preventing the uptake of oxygen. Warburg interpreted this effect as indicating the presence in cells of a cyanide-sensitive enzyme system (*Atmungsferment*) specially designed to activate molecular oxygen. The nature of this system, which even now is not fully understood, began to be elucidated after

decomposition of urea to ammonia and carbon dioxide, was affected by mercuric chlorido in the same way as were the bacteria which cause ammoniacal fermentation of urea. The concentration of mercuric chloride required to inhibit jack-bean urease was of the same order as that required to prevent ammoniacal fermentation by bacteria. The urea-splitting activity of the bacteria was, however, inhibited by concentrations of poisons which did not kill the bacteria. Inhibition of urease by mercuric chloride could be reversed by KCN. Jacoby, from a consideration of his results, suggested that three types of cell poisons could be distinguished :—

- (1) Poisons acting by damaging gross cell structure.
- (2) Poisons acting on reproduction and the synthesis of enzymes; the growth of a bacterial culture being inhibited when the synthesis of its enzymes is prevented.
- (3) Poisons acting directly by chemical combination with enzymes already present in the cell.

Jacoby's ideas differ little from those which we hold to-day, and experimental evidence has been slowly collected supporting and extending those ideas.

Among the pioneers, Rona in 1920 made a quantitative study of the effect of chemotherapeutic drugs on enzymes. Rigid control of *pH* provided reliable results for the action of quinine and its derivatives on invertase and serum lipase, and for seven arsenical drugs on urease and serum lipase (Rona and Gyorgy, 1920; Rona and Petow, 1920; Rona and Bach, 1920; Rona and Bloch, 1921; Rona and Reinicke, 1921). The arsenicals provided interesting examples of specificity; atoxyl and arsenic acid inhibited serum lipase but not urease, while methyl-arsenoxide inhibited urease but not lipase: atoxyl had no effect on lipase from guinea-pig serum, but was particularly active against human serum lipase. The toxicity of quinine and its derivatives was found to be directly dependent on *pH*, the results indicating that the free base is the toxic form of the drug.

The actual site of attack of arsenical drugs on enzymes

oxidation more than another. Exposure of *Escherichia coli* to copper sulphate, followed by washing, resulted in the elimination of many oxidising mechanisms which could be restored by treatment with hydrogen sulphide.

Quastel's next step was to obtain in cell-free stato the enzymes (known as dehydrogenases) which oxidised individual substrates, and he compared the action of antiseptics on those enzymes with their action on the intact cell. He followed this with valuable work, which will be discussed in Chapter VII, on the effect of the structure of antiseptics on their enzyme-inhibitory properties.

We have traced the growth of the idea that drugs act by inhibiting the normal enzymic reactions of the cell, and have now to see how far this theory can elucidate the mass of experimental data collected during the growth of chemotherapy. Before proof can be secured of the site of action of any particular drug, the enzymic processes which are assumed to be inhibited must be understood. At the time when Quastel was demonstrating the existence and inhibition of the dehydrogenating mechanisms of bacteria, the role of these dehydrogenases in metabolism was largely unknown. Since 1930 enzyme chemists have been concerned in elucidating the essential energy-yielding processes of the living cell; they have identified scores of enzymes and even obtained many in a highly purified crystalline state. The work has proceeded at such a pace that investigation of the action of drugs on enzymes has lagged behind the isolation of the enzymes themselves. Our best course, therefore, will be to outline in the rest of this chapter the present state of knowledge of the function of enzymes in intermediary metabolism, and in later chapters to interpret drug action in the light of this knowledge.

Nature of enzymes

All known enzymes are proteins with, so far as is known, much the same amino acid composition as other proteins. Many enzymes carry bound to the protein a relatively low molecular weight group, not linked by covalent bonds to the

Keilin (1925) had demonstrated the importance in living cells of iron porphyrin pigments to which he gave the name cytochrome. The oxidation of cytochrome in the living cell was found to be specifically inhibited by cyanide.

The specific action of cyanide was also demonstrated by Meyerhof (1917) in acetone-killed bacterial cells. Such cells had been shown by Cathcart and Hahn (1902) to reduce methylene blue in the absence of oxygen. Meyerhof found that inhibition of respiration by cyanide was much reduced by methylene blue, thus showing that the dye was taking the place of the cyanide-labile "Atmungsferment." The inhibition produced by narcotics was unchanged in the presence of methylene blue.

With the exception of one study on the inhibitory action of arsenic acid on cellular respiration (Onaka, 1910), little work on chemotherapeutic drugs was carried out by Warburg and his school, but the gap began to be filled in 1927 with the work of Quastel on the effect of antiseptics on metabolic processes of bacteria (Quastel and Wooldridge, 1927 *a* and *b*; Quastel and Wheatley, 1931; Quastel, 1931). The basis for this work was the fact that, in the presence of certain organic substances (known as substrates) which are broken down by cells, bacteria are capable of reducing anaerobically large quantities of methylene blue. This process Quastel attributed to "activation of the substrate" by specific enzymes of the organism. Exposure of bacteria to various antiseptics resulted in varying degrees of loss in capacity to oxidise individual substrates. Quastel's aim in this work is made clear in the statement . . . "Whether this experimental method will enable us to perceive precisely how an antiseptic exerts its lethal effect still remains to be seen, but it is clear that the method will allow us to compare and contrast the effects of certain lethal materials in a manner much more extensive than has hitherto been possible" (Quastel and Wooldridge, 1927). The toxicity of antiseptics, such as dyes, was not due to a general lethal action, since some activating mechanisms remained intact even after death of the cell, while specificity in action of dyes was also found—one dye inhibiting a certain

CELL METABOLISM

vital substances are produced. These vital substances the very enzymes involved in the activation, degradation, synthesis of intermediate metabolites; thus, an enormous number of events is involved in maintaining life. We recognize the existence of this chain but are still in the process of describing the individual links.

Cytochrome enzymes

During respiration in air, living cells use up oxygen and produce mainly carbon dioxide and water as the end products of metabolism. To account for the formation of water from oxygen, can catalyze the reaction $H_2 + \frac{1}{2}O_2 \rightarrow H_2O$. This reaction occurs with explosive rapidity if the temperature is raised to 700°-800° C., but in the absence of catalyst cannot proceed at temperatures of 20°-37° C. We know that the rate of a reaction is determined by the frequency with which the reacting molecules may surmount an energy barrier; this barrier may be regarded as energy essential for rearrangement of the atoms in each molecule to form an unstable configuration, known as the "activated" form. At room temperature the number of molecules which can achieve this "activated" form is negligibly small in the case of hydrogen and oxygen, and, in the absence of catalyst, reaction proceeds with immeasurable slowness. As the temperature is raised, the energy of each molecule is increased until a point is reached where a sufficient proportion of the molecules are "activated" for reaction to take place. In the presence of certain inorganic catalysts or of respiring cells, "activation" must also occur, since the reaction proceeds at considerable velocity.

The similarity between the inhibitory action of cyanide on cellular oxidation and on the aerobic oxidation of cysteine by artificial catalysts containing iron suggested to Warburg (1924) that the oxygen-activating system of living cells contained iron.

In 1925, during an examination of the thoracic muscles of certain insects, Keilin noted the existence of a pigment with characteristic absorption bands. The bands were

rest of the molecule and not built up from amino acids on the normal protein-peptide pattern. This group in some enzymes is sufficiently firmly bound to be regarded as part of the enzyme molecule, and is in these cases usually referred to as a *prosthetic group*. In other cases, the union is reversible, and in solution the enzyme exists with this group (known then as the *coenzyme*) largely in the free state. Families of enzymes are known which have a common prosthetic group or coenzyme. Each member of such a family differs from the others in its specific protein which determines the nature of the reaction catalysed. It follows that the protein must possess some unique configuration capable of exerting a special influence on both substrate and prosthetic group. The exact nature of this influence remains a matter for speculation; our ignorance on this point is covered by the statement that the substrate combines with, and is "activated" by, the "active centre" of the enzyme.

A fundamental problem faces any chemist investigating the reactions by which cells convert carbohydrates, fats or nitrogenous foodstuffs to water, to carbon dioxide or to the varying end products of cellular metabolism. Many of the substances involved are stable and most of the reactions involved cannot be carried out in the laboratory under physiological conditions. The biochemist therefore calls the useful word "activation" to his aid, and postulates that living cells have the ability to activate molecules through the use of enzymes. The exact physical forces involved in activation are unknown, but there is no doubt that enzymes, even when separated from the parent cells and transferred to the inhospitable environment of the chemical laboratory, can catalyse reactions with remarkable efficiency.

The energy liberated during the complete oxidation of a carbohydrate is considerable. The cell has evolved a whole series of integrated partial oxidations by which this energy is liberated or stored in small manageable packets; these are utilised for "coupled" reductions of other foodstuffs or to force essential synthetic or endothermic reactions by which

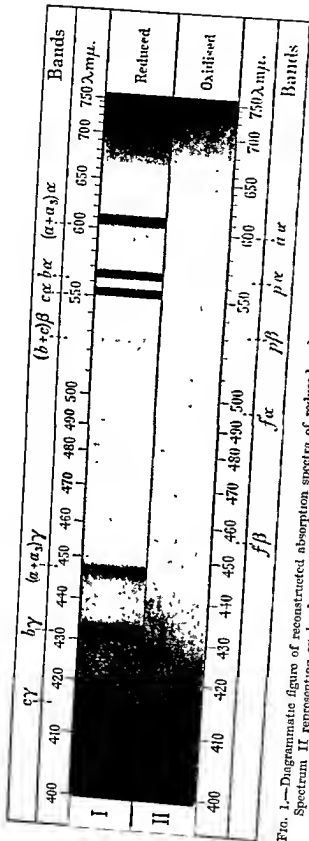


FIG. 1.—Diagrammatic figure of reconstructed absorption spectra of reduced and oxidized cytochrome in heart-muscle preparation. Spectrum II representing oxidized cytochrome, reconstructed from different depths of preparation, shows remains of reduced aa -band, two diffuse parametatin bands (pa and $p\beta$) of compounds b and c , and two diffuse bands (f) of a flavoprotein compound, which become hardly perceptible in preparations showing reduced cytochrome. (For full details see Keilin and Hartree, 1939.)

the insect struggled violently or when it was deprived of oxygen, and disappeared when oxygen was present and the insect quiescent. Keilin concluded that the observed spectrum was that of the reduced form of a respiratory pigment which in the oxidised form had no characteristic absorption bands. Cyanide, which inhibited all respiration, also inhibited oxidation of the reduced form of pigment. Keilin was later able to show from spectroscopic studies that there were at least three such pigments which he named *cytochromes a, b and c*. The cytochromes are widely distributed, occurring in animals, plants and micro-organisms, and their absorption spectra (Fig. 1) indicate that all three are haemochromogen pigments (Keilin, 1925, 1929, 1933).

The nature of cytochromes *a* and *b* is still unknown, as they have not been isolated, but they are probably mixtures of several components. Cytochrome *c*, which can be purified, has been found by Theorell to be a heat-stable haematin-protein of molecular weight 13,000; the porphyrin nucleus is firmly bound, probably through thioether linkages, to the protein. From degradative studies, Theorell has suggested the formula depicted in Fig. 2 (Theorell, 1938, 1941; Theorell and Åkesson, 1941).

Purified cytochrome *c* containing ferric iron can be reduced to the ferrous iron form by various reducing agents and re-oxidised by ferricyanide, but the reduced form is not oxidised at physiological pH by oxygen. In the living cell, reduced cytochrome *c* is readily re-oxidised in the presence of oxygen; hence there must be some system responsible for the physiological oxidation of reduced cytochrome. The nature of the enzyme which activates molecular oxygen and re-oxidises reduced cytochrome was indicated when Keilin found that cytochrome does not combine with cyanide or with carbon monoxide although both these poisons prevent its oxidation in the living cell. Carbon monoxide forms compounds with ferrous iron and particularly with iron porphyrins such as haemoglobin; in the case of haemoglobin such a compound is dissociated by light. Warburg (1926) showed that when the oxygen uptake of intact yeast cells was inhibited

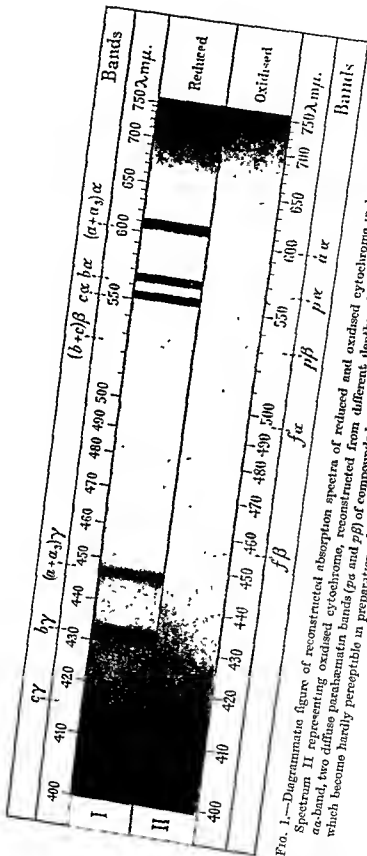


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by carbon monoxide and the poisoned cells were then exposed to light of suitable wavelength, respiration was resumed. The effectiveness of light in reversing the carbon monoxide inhibition varied with the wavelength used. If the absorption coefficient (*i.e.* the effectiveness of the light in restoring

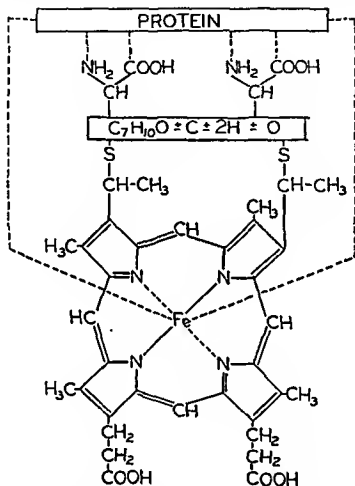


FIG. 2.—Structure of cytochrome *c*. (Theorell, 1941.)

respiration) was plotted against wavelength, a photochemical absorption curve was obtained closely similar to that of carboxy-haemoglobin (Warburg and Negelein, 1928). Warburg accordingly suggested that haemin iron in the form of a thermolabile enzyme (the *Atmungsferment*) played a vital part in respiration. Warburg's *Atmungsferment* is inhibited by

and Eichel, 1947). The spectrum of cytochrome oxidase has been provisionally identified by direct spectroscopy (Keilin and Hartree, 1939).

If we represent enzymic protein by a circle, "activated" oxygen by the symbol O_{Act} and the oxidised and reduced forms of cytochrome as (Fo^{+++}) and (Fo^{++}) respectively, the oxidation of reduced cytochrome in cellular metabolism can be depicted diagrammatically as in Fig. 3. The representation of the activated complex as containing 2 mols. of cytochrome is not intended to imply that the reaction is necessarily trimolecular. The source of the protons (H^+) will become evident when we extend our discussion to the biological mechanism for reduction of cytochrome to the (Fe^{++}) form.

Flavoprotein enzymes

Keilin showed by spectroscopic observation that in living cells cytochrome is reversibly reduced and oxidised, and, with cytochrome oxidase, provides a mechanism for the participation of molecular oxygen in respiration. If purified cytochrome *c* is reduced chemically and added to cytochrome oxidase preparations, in the presence of oxygen it is rapidly converted to the oxidised form, but in the absence of oxygen is not re-reduced, as it is in the living cell. The living cell must therefore possess a mechanism for the reduction of cytochrome *c*. A whole group of respiratory enzymes, known as flavoproteins, has been isolated and crystallised; some of these probably provide a mechanism for the *in-vivo* reduction of the cytochromes and can be used *in vitro* to reconstruct artificial systems in which the oxidation-reduction cycles of living cells are simulated.

The first flavoprotein to be isolated was the "old yellow enzyme," discovered by Warburg and Christian (1932) and later crystallised by Theorell (1935). By dialysis against dilute acid, the enzyme can be split into a soluble yellow prosthetic group, and a colourless protein which is insoluble in acid but redissolves on neutralisation. On addition of the yellow dialysate to the neutralised protein solution, the enzyme is rapidly reconstituted. The yellow prosthetic group

THE BASIS OF CHEMOTHERAPY

cyanide and by carbon monoxide and is thermolabile; the cellular system which catalyses the oxidation of reduced cytochrome *c* is also thermolabile, but cytochrome *c* itself is thermostable. These facts suggested to Keilin that the oxygen-activating enzyme (*Atmungsferment*) is responsible for the oxidation of reduced cytochrome by molecular oxygen in the living cell (Keilin, 1929). The enzyme was renamed

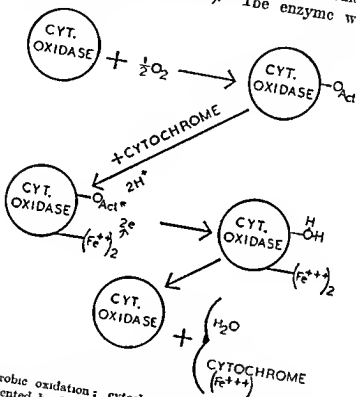


Fig 3—Aerobic oxidation; cytochrome system. (Oxidised cytochrome is represented by Fe⁺⁺⁺, reduced cytochrome is represented by Fe⁺⁺, electron transfer is represented by e⁻ →.)

cytochrome oxidase. Up to the present, all attempts to purify cytochrome oxidase have failed; even the preparation of a cell-free solution has proved difficult. Claims have been made for the success of a method involving supersonic disintegration of cell structure (Haas, 1943), but these are doubted by Keilin and Hartree (1947). Extraction with sodium desoxycholate has been said to produce a soluble preparation with high activity (Wainio, Cooperstein, Kollen

of cytochrome *c*, it is rapidly converted to the oxidised form, while cytochrome *c* is simultaneously reduced. The three proteins cytochrome reductase, cytochrome *c* and cytochrome oxidase therefore provide a limited system for the catalysis

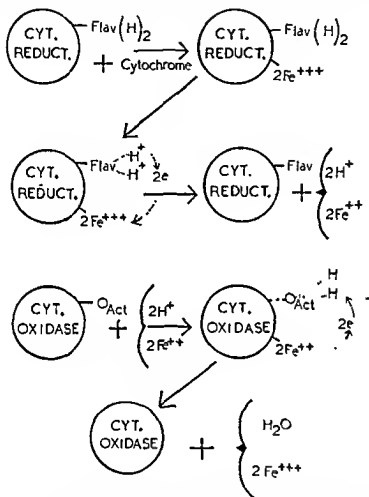
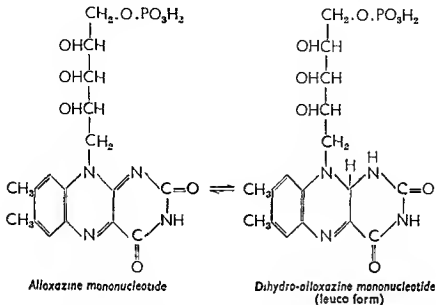


FIG. 4.—Aerobic oxidation; flavoprotein-cytochrome system. (Oxidised cytochrome is represented by Fe^{+++} , reduced cytochrome is represented by Fe^{++} , cytochrome reductase is abbreviated to CYT. REDUCT.)

of the reaction $\text{H}_2 + \frac{1}{2}\text{O}_2 \rightarrow \text{H}_2\text{O}$. The series of reactions involved is represented diagrammatically in Fig. 4, the reduced and oxidised forms of riboflavin being represented as $-\text{Flav H}_2$ and $-\text{Flav}$; other abbreviations are as in Fig. 3.

The second yellow enzyme which is believed to act through the cytochrome system is known as *diaphorase* and was

has been identified as alloxazine mononucleotide, the phosphoric ester of riboflavin, a member of the vitamin B complex (Review : Theorell, 1937).



The yellow solution of riboflavin phosphate is readily reduced by hyposulphite to the colourless "leuco" form, as indicated in the formulæ above. The "leuco" flavin is reoxidised to the yellow quinonoid form by shaking with air. The complete flavoprotein behaves in the same way and thus might act as a cellular catalyst for the transfer of hydrogen to molecular oxygen. However, the oxidation of the reduced enzyme in air is so slow that it is unlikely to be of much use to the cell and cannot account for more than a small fraction of the observed oxygen uptake of aerobic cells.

The "old yellow enzyme" is incapable of reducing cytochrome, but two other flavoproteins have been isolated which probably act as cellular reducing agents for the cytochrome system. *Cytochrome reductase*, isolated from yeast by Haas, Horecker and Hogness (1940), has the same molecular weight as the old yellow enzyme (78,000) and the same prosthetic group, but has quite distinct catalytic properties. The reduced "leuco" form of cytochrome reductase is not oxidised by molecular oxygen; but, if added to a solution

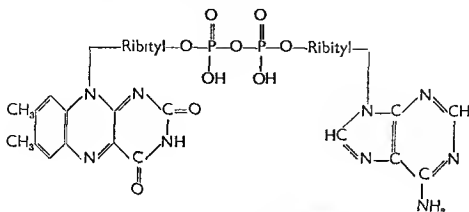
for reducing the flavin enzymes. It will be remembered how Quastel showed that bacteria were capable of dehydrogenating various normal metabolites anaerobically in the presence of methylene blue, which acted as a hydrogen acceptor. A whole group of enzymes, the *pyridine nucleotide dehydrogenases*, have since been identified as specific catalysts for the dehydrogenation of such metabolites. These dehydrogenases in turn reduce diaphorase or cytochrome reductase and thus act as catalysts for the aerobic oxidation of cellular metabolites.

Pyridine nucleotide dehydrogenases

We have already remarked on the controversy carried on for about twenty years between the adherents of the theories of Liebig and of Pasteur on the nature of enzymes. Much of the support for Pasteur's belief in the "vital" origin of ferments depended on the fact that all early experiments designed to produce fermentation in the absence of living cells had failed. Berthelot, it will be remembered, expressed the view that organisms were not themselves ferments but rather the producers of ferments, but he had been unable to ferment sugar and produce carbon dioxide and alcohol in the absence of living cells. A method of preparation from yeast of a cell-free filtrate capable of fermenting sugar was discovered by Buchner (1897). Buchner concluded that "the production of alcoholic fermentation does not require so complicated an apparatus as the yeast cell, and that the fermentative power of yeast-juice is due to the presence of a dissolved substance—Zymase." Harden and Young (1906) showed that Buchner's juice could be separated into a thermolabile protein component and a thermostable dialysable component to which they gave the name *Co-zymase*. Neither component was active by itself, but together they constituted the whole activity of zymase.

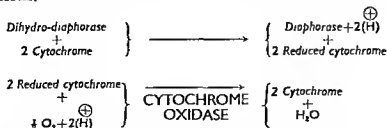
The nature and function of *Co-zymase*, or as it was later called, *coenzyme I*, remained something of a mystery for more than twenty years. From 1925 to 1935 methods were gradually worked out for its purification, and it was finally identified as

purified by Straub (1939). Its prosthetic group was identified as alloxazine adenine dinucleotide.



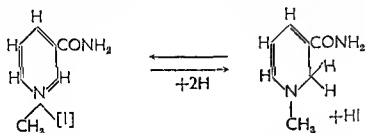
Alloxazine adenine dinucleotide

Diaphorase, like cytochrome reductase, can be reduced to a colourless leuco-form which does not re-oxidise on shaking with air, but reduced diaphorase fails to react with cytochrome c. When added to the complete cytochrome-cytochrome oxidase system, reduced diaphorase is, however, extremely rapidly oxidised by a cyanide-sensitive heat-labile enzyme system, which is presumably one of the group of *a* or *b* cytochromes. The transfer of hydrogen from the dihydro-isalloxazine group of reduced diaphorase to molecular oxygen may be represented by the following linked series of reactions.



These flavin enzymes are widely distributed in the cells of animals and micro-organisms and, with the cytochrome system, provide a catalytic mechanism for the participation of oxygen in cellular metabolism under physiological conditions. If this system is to work, the cell must also possess methods

mode of action (Warburg, Christian and Griesse, 1935). Both diphosphopyridine nucleotide and triphosphopyridine nucleotide have characteristic absorption spectra, and both undergo a similar change in spectrum when reduced with alkaline hyposulphite. Reduction involves the uptake of two hydrogen atoms; its nature was indicated when nicotinamide methiodide was shown to undergo a similar reduction with similar change in absorption spectrum (Karrer, Kahnt, Epstein, Jaffé and Ishii, 1938; Karrer, Ishii, Kahnt and van Bergen, 1938). This reduction of the methiodide can be represented as follows :



Warburg found that coenzyme II showed a change in absorption spectrum when added to a solution of red cell enzyme + glucose-6-phosphate; in other words, an enzyme existed in blood corpuscles capable of catalysing the transfer of hydrogen from glucose-6-phosphate to triphosphopyridine nucleotide, so bringing about the oxidation of glucose-6-phosphate. The enzyme, known as glucose-phosphate dehydrogenase, was also found to occur in yeast (Warburg, Christian and Griesse, 1935; Negelein and Haas, 1935; Negelein and Gerischer, 1936). If purified glucose-6-phosphate dehydrogenase is added to a solution of glucose-6-phosphate and triphosphopyridine nucleotide, glucose-6-phosphate is converted to phosphogluconic acid only in so far as there is unreduced triphosphopyridine nucleotide available to act as hydrogen acceptor. Dihydro-triphosphopyridine nucleotide is not capable of transferring hydrogen directly to molecular oxygen, but requires cytochrome reductase to accept its hydrogen. In fact, the two flavin enzymes, diaphorase and cytochrome reductase, act as specific catalysts for the transfer of hydrogen from reduced coenzymes I and II through the cytochrome system to oxygen. The system for the oxidation

a pyridine adenine dinucleotide with the structure shown in Fig. 5A (Euler and Schlenk, 1937).

While the work on coenzyme I was still incomplete, Warburg and Christian (1931) discovered a different thermostable coenzyme in red blood cells. They found that laked

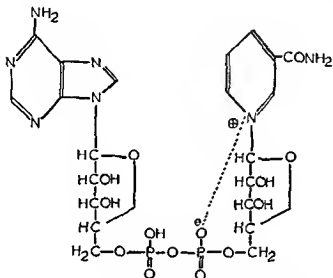


FIG. 5A.—Coenzyme I (diphosphopyridine nucleotide).

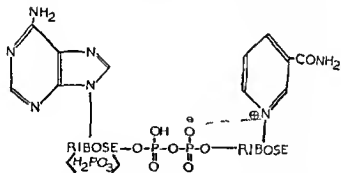


FIG. 5B.—Coenzyme II (triphosphopyridine nucleotide).

horse erythrocytes gave an enzyme system capable of oxidation of glucose-6-phosphate, and separated the system into a thermolabile enzyme and a thermostable substance, *coenzyme II*, which resembled, but was not replaceable by, *coenzyme I*. Warburg isolated *coenzyme II*, determined its structure (triphosphopyridine nucleotide, Fig. 5B) and elucidated its

system plays no part in these "linked" oxidation-reductions is indicated by the absence of any cytochrome absorption bands in suspensions of certain bacteria. Bacteria may be classed as aerobes, facultative anaerobes (which can utilise oxygen but may be able to grow in its absence) and strict anaerobes (which only grow when oxygen is completely excluded). The accompanying Table 1 shows the occurrence of cytochrome in some bacteria in each of these classes. Among the facultative anaerobes one or more of the absorption bands of the cytochrome complex is often found to be missing, while in the strict anaerobes no cytochrome bands are visible.

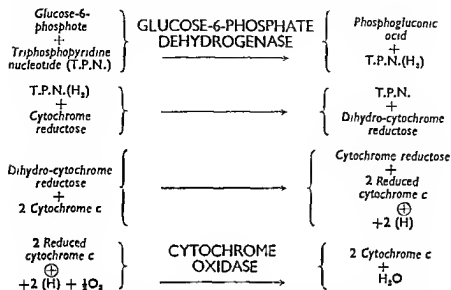
TABLE 1
Distribution of cytochromes in bacteria

Organism	Respiratory Character	Cytochromes
<i>B. anthracis</i> . . .	Aerobe	Present
<i>M. tuberculosis</i> . . .	Aerobe	Present
<i>S. aureus</i> . . .	Aerobe	Present
<i>V. cholerae</i> . . .	Aerobe	Present
<i>E. typhosa</i> . . .	Facultative anaerobe	Partially present
<i>S. dysenteriae</i> . . .	Facultative anaerobe	Partially present
<i>L. delbrueckii</i> . . .	Facultative anaerobe	Absent
<i>Cl. welchii</i> . . .	Anaerobe	Absent
<i>Cl. tetani</i> . . .	Anaerobe	Absent

(Adapted from Stephenson, 1939)

The presence of pyridine nucleotides and their dehydrogenases in both aerobic and anaerobic cells, coupled with the absence of the cytochrome system from anaerobic cells, suggests similarity in the metabolic pathways in both types of cells up to a common point; beyond this point in aerobic cells the cytochrome system evidently takes over. As we have seen, aerobic cells contain two important flavoprotein enzymes which are specifically designed to convert the dihydro-pyridine nucleotides to the oxidised form through the cytochrome system, so making the two coenzymes available for further reaction with dehydrogenase and metabolite. Anaerobic cells must achieve the same re-oxidation of dihydro-pyridine nucleotides by other means. An example of such a mechanism is provided by the dehydrogenase which catalyses the dehydrogenation

of glucose-6-phosphate to phosphogluconic acid and water may then be represented diagrammatically as follows:—



Glucose-6-phosphate dehydrogenase is only one of a large group of enzymes which catalyse the transfer of hydrogen from metabolite to one of the pyridine nucleotides. Many of these enzymes, known collectively as the pyridine nucleotide dehydrogenases, have been isolated in crystalline form (see review, Schlenk, 1945). By activating metabolites they provide the first link in a chain of oxidation-reduction reactions which results in a stepwise transfer of hydrogen from cellular metabolite to molecular oxygen as indicated in the above scheme. They do much more than this however, since they function in anaerobic as well as in aerobic metabolism.

We have already noted that under anaerobic conditions, but in the presence of methylene blue, both animal and bacterial cells can catalyse the oxidation of metabolites with simultaneous reduction of methylene blue to the "leuco" form. Living anaerobic cells obviously cannot utilise methylene blue as their biological hydrogen acceptor. Nevertheless, in a closed anaerobic system, each oxidative step must be accompanied by a corresponding reduction, and cells capable of anaerobic metabolism must possess means for the removal of hydrogen from reduced coenzymes. That the cytochrome

of conversion of nucleotide to dihydro-nucleotide. The point where the curve flattens represents the equilibrium point for the original mixture. If, after equilibrium has been reached, more alcohol is added to the system, the extinction coefficient is increased, thus indicating further conversion of nucleotide to dihydro-nucleotide; if aldehyde is added the opposite effect is observed.

The equilibrium constant (K) for the reaction may be calculated from such spectrophotometric data (Negelein and Wulff, 1937). According to the law of mass action,

$$\frac{[\text{D.P.N.}]}{[\text{D.P.N.H}_2]} \frac{[\text{Alcohol}]}{[\text{Aldehyde}]} = K$$

(concentration of reactants is indicated by []). At pH 7.0 and 38°, K was calculated to be 2.14×10^4 . This means that when the coenzyme is half reduced, i.e. when

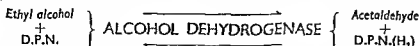
$$[\text{D.P.N.}] = [\text{D.P.N.H}_2], \text{ the value } \frac{[\text{Alcohol}]}{[\text{Aldehyde}]} = 2.14 \times 10^4$$

In other words the equilibrium is greatly in favour of accumulation of alcohol, a concentration of 2.14×10^4 mols. of alcohol per mol. of aldehyde being possible. Under physiological conditions, therefore, the reaction will proceed in the direction of alcohol formation with consequent conversion of reduced pyridine nucleotide to the oxidised form. Acetaldehyde, as we shall see, is one of the main intermediary products of anaerobic fermentation; its reduction to alcohol thus provides a method for the anaerobic removal of hydrogen from dihydro-diphosphopyridine nucleotide. What is in reality occurring is an oxidation of one substrate coupled with simultaneous reduction of another.

Metabolism of carbohydrate brought about in the absence of oxygen is called *fermentation*, the particular type of fermentation taking its name from the predominant end-product; thus, alcoholic fermentation, acetic acid fermentation, propionic acid fermentation, acetone fermentation, lactic acid fermentation, butyric acid fermentation, and so on.

The question might well be asked, what does the cell gain by fermentation? Carbohydrate seems to be the main

of alcohol to acetaldehyde. This enzyme has been isolated from yeast cells in crystalline form, and requires diphosphopyridine nucleotide as a coenzyme (Negelein and Wulff, 1937). The reaction involved in the oxidation of alcohol can be represented as



Like most enzymic reactions, the reaction is reversible; the direction depends on the amounts of the reactants present and

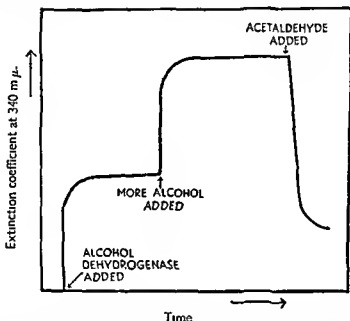
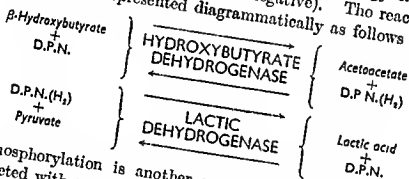


FIG. 6 — Reversible oxidation and reduction of diphosphopyridine nucleotide by alcohol dehydrogenase in the presence of alcohol or acetaldehyde. Starting mixture contains diphosphopyridine nucleotide and alcohol. (Adapted from Euler, Adler and Helstrom, 1936)

on external conditions such as pH and temperature. The course of the reaction in an isolated and purified preparation can be readily followed spectrophotometrically since the reduced form of coenzyme has a distinct absorption band at 340 mμ which disappears on oxidation. If purified dehydrogenase, alcohol and excess diphosphopyridine nucleotide are mixed and the change in extinction coefficient with time is plotted (Fig. 6), a curve is obtained representing the degree

energy of the system. Such an endergonic reaction is thermodynamically impossible without a source of energy. This is the case even in the presence of an enzyme, since by definition, an enzyme can only catalyse a thermodynamically-possible reaction. Nevertheless lactic acid is an end-product derived from pyruvic acid in fermentation of sugars. The possibility of energetic coupling of pyruvic acid reduction with oxidation of β -hydroxybutyric acid (an exergonic reaction) has been shown by Green, Dewan and Leloir (1937). Pyridine nucleotide dehydrogenases are catalysts for both reactions, and the common coenzyme I links them. The oxidation of β -hydroxybutyrate provides both the energy and the hydrogen necessary for the reduction of pyruvate, and the formation of lactate is made possible because the overall energy change of the system is negative (ΔF is negative). The reactions involved can be represented diagrammatically as follows:—



Phosphorylation is another process which is intimately connected with energy transfer in cell metabolism. We have mentioned that lysed red cells contain the enzyme glucose-6-phosphatase dehydrogenase, which in the presence of coenzyme II oxidises glucose-6-phosphatase to phosphogluconic acid. The dehydrogenase cannot oxidise glucose itself, although intact red cells do so. Such a result implies that the cells possess, in addition to a system for the oxidation of glucose-6-phosphatase, an enzyme capable of converting glucose to glucose-6-phosphatase. The reaction glucose + phosphoric acid \rightarrow glucose-6-phosphatase is endergonic; the intact cell must therefore possess a means of transferring energy from an energy-yielding reaction in order to bring about the phosphorylation of glucose.

Warburg and Christian (1939) were able to demonstrate

energy-provider of metabolism, the free energy change in the complete oxidation of glucose to carbon dioxide and water being 686 kg. cal./mol. In the absence of oxygen, the cell is forced to obtain energy by carrying out either molecular rearrangements which involve gain in free energy, or coupled reactions in which energy released by one change is utilised to force another reaction. The overall energy yield in these cases is very much less than in total oxidation; ethyl alcohol fermentation makes available only 7.9 per cent. of the total energy of aerobic oxidation, while the most efficient fermentation, that giving rise to propionic acid, only yields 79 kg. cal. per gram mol. The rest of the potential energy of combustion remains unused in the waste products of fermentation. This great waste of energy is probably compensated for by the independence of oxygen supply which the cell gains through adopting this mode of life.

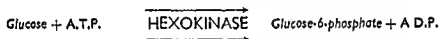
Energy transfer and organic phosphate

Many micro-organisms are able to grow on media consisting of inorganic salts plus a single organic compound such as glucose, glycerol or acetic acid. During growth, protein, polysaccharide, fat and all the various complex organic molecules which go to make up the living cell are synthesised. Many reactions of these synthetic processes involve an increase in free energy, and may only occur if coupled in some way with reactions able to supply the necessary energy. The nature of the energetic coupling between energy-liberating (*exergonic*) reactions and energy-consuming (*endergonic*) reactions is therefore a fundamental problem of cellular metabolism (Fruton, Ball, Bergmann, Kalckar, Meyerhof and Smythe, 1944; Lipmann, 1946b). It is incidentally of considerable interest in any study of the mode of action of drugs, since certain cell poisons inhibit cell synthesis without inhibiting oxidation (Clifton and Logan, 1939; Hotchkiss, 1944; Spiegelman and Kamen, 1946).

One method of energetic coupling has already been mentioned, linked oxidation-reduction. In the reduction of pyruvic acid to lactic acid there is an increase in the free

The formation of adenosine triphosphate from adenosine diphosphate and phosphoric acid is endergonic, so also is the formation of diphosphoglyceric acid from phosphoglyceric acid and phosphoric acid. The necessary energy for the uptake of inorganic phosphate is supplied by the oxidation of aldehyde to acid and this energy is transferred to adenosine diphosphate with transfer of the phosphate group. Adenosine triphosphate may then be considered to contain an "energy-rich" phosphate bond.

An enzyme, hexokinase, has also been purified and crystallised, which, in the presence of a thermostable coenzyme identified as adenosine triphosphate, is capable of catalysing the phosphorylation of glucose (Berger, Slein, Colowick and Cori, 1946; Kunitz and McDonald, 1946). As already



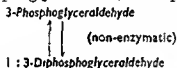
mentioned, the phosphorylation of glucose by inorganic phosphate is an endergonic reaction but, in the presence of hexokinase and adenosine triphosphate, glucose is phosphorylated with simultaneous evolution of heat. The energy for the reaction is provided by the energy-rich phosphate of adenosine triphosphate which is transferred to glucose, while adenosine triphosphate is converted to adenosine diphosphate.

There occur in the living cell various organic compounds of phosphorus in which it is possible to distinguish two types of phosphate bond (Lipmann, 1941; Kalckar, 1941). Where phosphoric acid is linked to an alcoholic hydroxyl, as in the sugar phosphates, the free energy change on hydrolysis is only of the order of 1 to 3 kg. cal. per mol. If phosphoric acid is linked to nitrogen as in creatine phosphate, to a carboxyl group as in diphosphoglyceric acid, or to another phosphate group as in adenosine triphosphate, the free energy change on hydrolysis is very much greater, being of the order of 8-10 kg. cal. per mol. These compounds contain the energy-rich phosphate bonds referred to previously. Adenosine triphosphate appears to function as a carrier and reserve of energy-rich phosphate bonds, and by its intervention

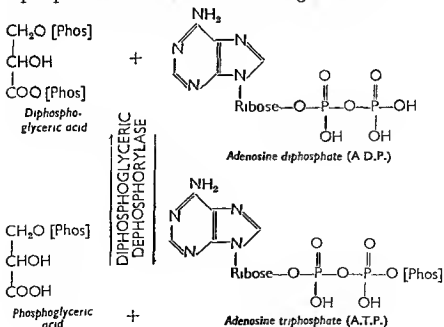
coupling of an exergonic oxidative reaction with an endergonic uptake of inorganic phosphate. The phosphate, by a mechanism of phosphate transfer, was made available for the phosphorylation of hexoso. Phosphoglyceraldehyde, in the presence of inorganic phosphate and its specific dehydrogenase is oxidised and phosphorylated to diphosphoglyceric acid. Diphosphopyridine nucleotide acts as coenzyme and hydrogen acceptor. The exact mechanism of phosphate uptake is not



quite clear; Warburg suggests that 3-phosphoglyceraldehyde forms a loose addition compound with phosphoric acid prior to oxidation. Diphosphoglyceric acid, in the presence of adenosine



diphosphate and a specific dephosphorylating enzyme (crystallised by Bucher, 1942), is transformed to monophosphoglyceric acid, the phosphate group being transferred to adenosine diphosphate as indicated in the following scheme:—



(Herbert, Gordon, Subrahmanyam and Green, 1940) and forms glyceraldehyde phosphate and dihydroxyacetone phosphate. Dihydroxyacetone phosphate is not further degraded as such, but is immediately rearranged by the enzyme isomerase to glyceraldehyde phosphate with the nett result that two molecules of glyceraldehyde phosphate are formed from one of fructoso diphosphate. The series of reactions up to this point may be represented conveniently as in Fig. 7 in the form used by Lipmann (1941).

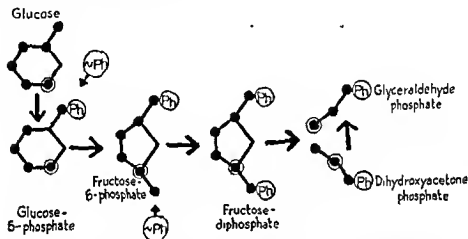
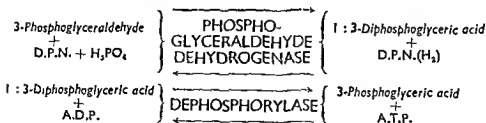


FIG. 7.—Anaerobic breakdown of glucose to triose phosphate [$\sim\text{Ph}$ = energy-rich phosphate bond]. (Lipmann, 1941).

The oxidation of phosphoglyceraldehyde to 3-phosphoglyceric acid with generation of an energy-rich phosphate bond has already been described (p. 66). It can be summarised as follows :—



The adenosino triphosphate formed at this stage is available for the phosphorylation of a further molecule of hexose. The system described obviously provides for a repetitive cycle of events by which endergonic reactions can proceed at the expense of linked exergonic reactions.

as a coenzyme many endergonic synthetic reactions become possible. The adenosine diphosphate formed in these reactions is then reconverted to adenosine triphosphate by exergonic reactions involving formation of further energy-rich phosphate bonds. Here we have the "manageable packets of energy," which, earlier in this chapter, we put forward as the mechanism adopted by the cell for storage or transfer of energy. The energy transferred with one energy-rich phosphate bond amounts to about one-fiftieth of that liberated by total oxidation of one carbohydrate molecule.

As we consider in detail the metabolism of cells and the interplay of oxidation-reduction and phosphorylation in this metabolism, the methods adopted in the living cell for the accomplishment of synthetic reactions should become more fully evident.

Anaerobic carbohydrate breakdown

Preliminary phosphorylation appears to be essential for the greater part of anaerobic breakdown of carbohydrate. The phosphorylation, if endergonic, may be carried out at the expense of energy derived from later stages, adenosine triphosphate acting as the energy- and phosphate-carrier by means of its energy-rich phosphate bonds. Whatever the type of carbohydrate, whether polysaccharide, disaccharide or monosaccharide, it can be transformed into fructose diphosphate before being degraded. In the case of glucose, the first stage has already been discussed, conversion by the enzyme hexokinase to glucose-6-phosphate. The enzyme phosphohexose isomerase (Meyerhof and Beck, 1944) catalyses the next step, rearrangement of glucose-6-phosphate to fructose-6-phosphate (see Fig. 7). A second phosphate group, also derived from adenosine triphosphate, is then introduced by the enzyme phosphohexokinase. The reaction product, fructose diphosphate, thus requires for formation from glucose two energy-rich phosphate bonds which must be provided in the form of adenosine triphosphate derived through linked exergonic reactions.

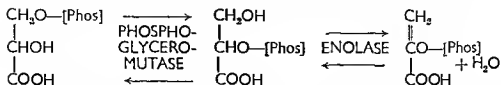
Fructose diphosphate is split by the enzyme zymohexase

TABLE 2

Anaerobic breakdown of glucose

Reaction	Enzyme	Isolation of Enzyme
Glucose + A.T.P. ↓ Glucose-6-phosphate + A.D.P.	Hexokinase	Metalloprotein (magnesium). Crystallised by Kunitz and Macdonald (1946), and by Berger, Stein, Colowick and Cori (1946)
Glucose-6 phosphate ↓ Fructose-6-phosphate	Phosphohexose isomerase	Partially purified by Meyerhof and Beck (1944)
Fructose-6-phosphate + A.T.P. ↓ Fructose-1 : 6-diphosphate + A.D.P.	Phosphohexokinase	Not purified
Fructose-1 : 6-diphosphate ↓ Glyceraldehyde-3-phosphate + dihydroxyacetone phosphato	Zymohexase (Aldolase)	Metalloprotein (zinc, iron, cobalt, or copper). Crystallised by Warburg and Christian (1943)
Dihydroxyacetone phosphate ↓ Glyceraldehyde phosphate	Triosephosphate isomerase	Purified by Meyerhof and Beck (1944)
1 : 3-Diphosphoglyceraldehyde + D.P.N. ↓ 1 : 3-Diphosphoglyceric acid + D.P.N. (H ₂)	Phosphoglyceraldehyde dehydrogenase	Crystallised by Warburg and Christian (1939), and by Cori, Stein and Cori (1945)
1 : 3-Diphosphoglyceric acid + A.D.P. ↓ 3-Phosphoglyceric acid + A.T.P.	Diphosphoglyceric dephosphorylase	Crystallised by Bucher (1942)
3-Phosphoglyceric acid ↓ 2-Phosphoglyceric acid	Triosemutase (Phosphoglyceromutase)	Not purified
2-Phosphoglyceric acid ↓ 2-Phosphoenolpyruvic acid	Enolase	Metalloprotein (magnesium, manganese or zinc). Crystallised by Warburg and Christian (1941, 1942)
2-Phosphoenolpyruvic acid + A.D.P. ↓ Pyruvic acid + A.T.P.	Phosphopyruvate dephosphorylase	Metalloprotein (magnesium, and possibly potassium). Lardy and Ziegler (1945). Crystallised by Kubowitz and Ott (1944)

3-Phosphoglyceric acid is not an end-product of anaerobic metabolism, but is further transformed by the enzyme phosphoglyceromutase to 2-phosphoglyceric acid, and this compound with the enzyme enolase is dehydrated to phosphoenolpyruvate.



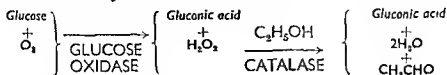
The intra-molecular rearrangement of 3-phosphoglyceric acid has created in phosphoenolpyruvate an energy-rich phosphate bond. Once more, adenosine diphosphate is a recipient of this energy, forming adenosine triphosphate and pyruvic acid under the influence of a dephosphorylating enzyme. The adenosine triphosphate is then available as a source of energy to force other desirable endergonic reactions.



The production of two molecules of pyruvic acid from one molecule of hexose has involved utilisation of two energy-rich phosphate bonds and formation of four of these bonds, so that, overall, two energy-rich phosphate bonds are generated by this anaerobic phase of carbohydrate breakdown. It will perhaps be helpful at this point to draw up a table of the reactions involved (Table 2). The enzymes concerned are also listed; a number of them have been isolated, purified and crystallised, and several have been found to be metalloproteins.

Phosphorylative breakdown of carbohydrates has been shown to occur in trypanosomes and malaria parasites, as well as in yeast and bacteria (Chen and Geiling, 1946; Speck and Evans, 1945a; Evans, 1946). It is therefore probable that the various reactions described in Table 2 are common to the majority of unicellular organisms as well as to higher animals, but they do not necessarily represent the *only* available pathway for carbohydrate breakdown. Pyruvic acid is, however,

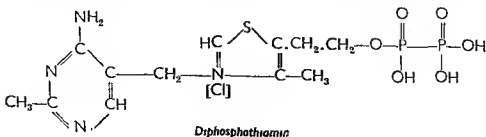
oxidase, have also been purified and identified as flavoproteins (Ball, 1939). Hydrogen peroxide is highly toxic to most living cells, and if produced by the aero-dehydrogenases must be destroyed instantaneously. Keilin and Hartree (1945) have suggested that oxidation by the aero-dehydrogenases is coupled with oxidation of other substrates, such as alcohols, through the enzyme catalase, a hæmatin-protein enzyme which occurs in all aerobic cells. The complete reaction for glucose oxidase could then be represented as follows :—



Degradation of pyruvic acid

The pyruvic acid molecule is highly reactive and participates in a wide variety of biological reactions. Barron (1943) has suggested that it should be regarded as the "hub towards which converge carbohydrates, fats and proteins in their catabolic and anabolic reactions." It can probably be regarded also as the dividing point between aerobic oxidative pathways involving complete oxidation of foodstuffs to carbon dioxide and water, and the more wasteful anaerobic metabolisms involving accumulation of such metabolic fragments as lactic acid, acetic acid, alcohol, butyric acid and so on.

At present, the cellular metabolism of pyruvate is incompletely understood and the enzyme systems concerned have not been studied with the same intensity as the enzymes of glycolysis. Diphosphothiamin (*co-carboxylase*) plays an essential part in many of these enzymic reactions, but the exact way in which it participates is unknown (*cf.* Karrer and Viscontini, 1946).



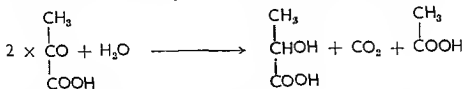
a key substance for various types of metabolism and from it arises, according to the organism and type of respiration, a multitude of intermediate metabolites.

Aerobic Carbohydrate Breakdown

Phosphorylative degradation, as described in the preceding section, is probably common to both aerobic and anaerobic cells, but an alternative phosphorylative pathway for glucose oxidation in aerobes certainly exists. Unicellular and multicellular organisms possess, as already mentioned, a pyridine-nucleotide enzyme, glucose-6-phosphate dehydrogenase, which oxidises its substrate to phosphogluconic acid. Dickens (1936, 1938) suggests that phosphogluconic acid then undergoes a series of decarboxylations and oxidations with final production of pyruvic acid. Little is known about the importance of this non-fermentative oxidation, but it should be kept in mind as an example of an alternative metabolic pathway which may play a greater or lesser part in cellular economy, according to environmental conditions. Certain micro-organisms are able to oxidise glucose, although unable to ferment it, and some of these are even unable to utilise pyruvate anaerobically (Barron and Friedemann, 1941).

Other aerobic micro-organisms are capable of direct oxidation of carbohydrate without preliminary phosphorylation, but the relative importance of such non-phosphorylative oxidation is unknown. An enzyme glucose oxidase or notatin, a flavoprotein, has been isolated from the mould *Penicillium notatum* (Coulthard, Michaelis, Short, Sykes, Skrimshire, Standfast, Birkinshaw and Raistrick, 1945). The enzymes catalysing subsequent stages in non-phosphorylative oxidation are unknown and the nature of the oxidative pathway can only be surmised (Tamiya, 1942; Muller, 1929). Glucose oxidase oxidises glucose to gluconic acid, and is capable of transferring hydrogen from metabolite directly to molecular oxygen without intervention of the cytochrome system; in which case hydrogen peroxide is produced. This is characteristic of a group of enzymes known as *aero-dehydrogenases*; other members of the group, such as xanthine

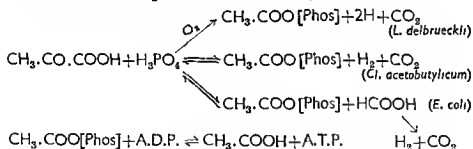
Acetic acid may arise by a dismutation reaction in which one molecule of pyruvate is oxidised, while a second is reduced to lactic acid. The enzyme catalysing this reaction has not



been purified, but diphosphothiamin seems to be involved as a coenzyme.

Pyruvate may also be decarboxylated by oxidative reactions which usually produce acetic acid. In bacteria, preliminary conjugation of pyruvate with phosphate may occur, with acetyl phosphate formed as a labile intermediate product. This type of reaction is known as *phosphoroclastic splitting* (review, Lipmann, 1946a). The overall reaction varies with conditions and bacterial species, but acetyl phosphate is formed in all cases; it may be converted to acetic acid, or may condense directly with other carbon compounds to give 4 or 6 carbon fragments.

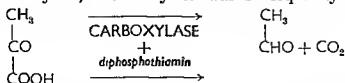
Three known types of phosphoroclastic splitting of pyruvate by bacteria are compared in the following equations:—



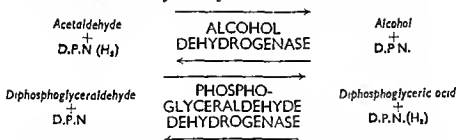
The top equation represents the first steps in the aerobic conversion of pyruvic acid to acetic acid and carbon dioxide by *Lactobacillus delbrueckii*. The reaction only proceeds in the presence of oxygen and phosphate; acetyl phosphate has been isolated as a crystalline salt from the reaction medium by Lipmann (1944). Hydrogen is removed by some unknown hydrogen acceptor.

The other two equations depict the mechanism of anaerobic transformation of pyruvate to acetic acid, carbon dioxide and

Diphosphothiamin was identified by Lohmann and Schuster (1937) as an essential coenzyme for the enzyme system in yeast which catalyses the anaerobic decarboxylation of pyruvic acid (carboxylase). Carboxylase was subsequently purified



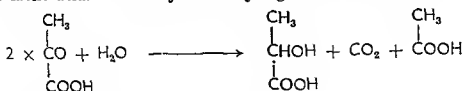
and found to require magnesium as well as co-carboxylase (Green, Herbert and Subrahmanyam, 1941). In the absence of oxygen, the acetaldehyde formed from pyruvate is reduced to alcohol by alcohol dehydrogenase, hydrogen being provided by dihydro-diphosphopyridine nucleotide derived, for example, from oxidation of diphosphoglyceraldehyde (see p. 66). As we have noted, this reaction provides a possible mechanism for the re-entry of pyridine nucleotide into the anaerobic cycle at the phosphoglyceraldehyde stage. For each molecule of phosphoglyceraldehyde oxidised to phosphoglyceric acid, one molecule of acetaldehyde may be reduced to alcohol.



Many types of cells do not produce alcohol as the main end-product of fermentation, but a number of other fermentation products can also be accounted for by the varied reactions of pyruvate metabolism. Lactic acid is produced from pyruvic acid by a reduction again involving dihydrodiphosphopyridine nucleotide, so providing another route by which the pyridine nucleotide can be regenerated. The enzyme (lactic dehydrogenase) from animal cells has been crystallised (Straub, 1940).



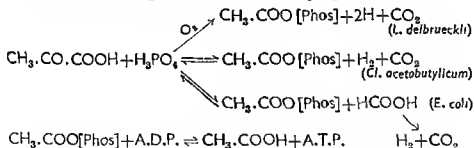
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The other two equations depict the mechanism of anaerobic transformation of pyruvate to acetic acid, carbon dioxide and

hydrogen. *Escherichia coli* forms formic acid as an intermediate product and decomposes it by the enzyme formic hydrogenlyase; *Clostridium acetobutylicum* forms carbon dioxide and hydrogen directly. Diphosphothiamin and magnesium or manganese have been shown to be essential factors for the reaction in *E. coli*. Here again, labile acetyl phosphate has been demonstrated to be a preliminary product in both cases (Koepsell and Johnson, 1942; Kalnitsky and Werkman, 1943; Utter and Werkman, 1944).

Acetyl phosphate contains an energy-rich phosphate bond, which can be transferred to adenosine diphosphate, allowing the energy released by decarboxylation to be utilised for endergonic reactions. The process may be reversed, and pyruvate may be formed from acetate and carbon dioxide; in this case energy is supplied by adenosine triphosphate. The occurrence of such a process has been directly proved in cell-free extracts of *E. coli*, which do not contain formic hydrogenlyase. These extracts form pyruvate either from formate and acetyl phosphate or from formate, acetate and adenosine triphosphate (Lipmann and Tuttle, 1945; Utter, Lipmann and Werkman, 1945). In all decarboxylation reactions, equilibrium is in favour of carbon dioxide formation, so that rapid removal of pyruvic acid must be effected to induce the reverse reaction.

Direct oxidative decarboxylation of pyruvate without intermediate phosphorylation occurs in micro-organisms and in animal tissue (Stumpf, 1945). This reaction is strongly inhibited by fluoroacetate, which acts as a specific inhibitor of acetate oxidation and probably prevents pyruvate breakdown by causing an accumulation of acetic acid (Bartlett and Barron, 1947; Kalnitsky and Barron, 1947). Fluoroacetate had no effect on acetyl phosphate formation by *E. coli*, and only partially inhibited pyruvate oxidation by *E. coli*, gonococci and *Corynebacterium creatinovorans*. In these organisms, at any rate, pyruvate evidently need not necessarily be metabolised directly to acetate.

The exact course of pyruvic acid decarboxylation in animal cells is less clear than in micro-organisms. The use of fluoroacetate suggested that a large proportion of pyruvate

oxidation goes through acetate (Bartlett and Barron, 1947). The formation of acetyl phosphate has not yet been demonstrated; because of the universal occurrence of an enzyme which splits acetylphosphate with great rapidity, its participation in pyruvate metabolism cannot be easily proved (Lipmann, 1946a). It is, however, reasonable to assume that pyruvate breaks down in animal cells to a two-carbon compound which might be acetate or the acetyl radical (see review, Bloch, 1947).

Condensation of pyruvic acid; tricarboxylic acid cycle and cellular synthesis

The reactions of pyruvate already discussed are part of the energy-yielding mechanisms of cellular metabolism, and the energy made available by these reactions can be utilised for the synthesis of new protoplasm. Pyruvate is not only a key substance in exergonic reactions, but also performs an essential part as a building block for the formation of carbohydrates, fats and proteins. The reactions involved are by no means fully understood, and the majority of the enzymes catalysing amino acid and fat synthesis have yet to be isolated; the best that we can do is to sketch an indistinct outline of the pattern of cell synthesis.

Micro-organisms will not grow if completely deprived of carbon dioxide by a rapid stream of carbon dioxide-free air. This failure to grow is probably associated with the failure of the synthetic process of carbon dioxide fixation. The existence of such a process in non-photosynthetic organisms was indicated when Wood and Werkman (1938) showed that during fermentation of glycerol by propionic acid bacteria, a stoichiometric relationship existed between carbon dioxide utilisation and succinic acid formation. Pyruvic acid was known to be an intermediate product in this fermentation, and the suggestion was put forward that pyruvate combined with carbon dioxide to form oxaloacetic acid, which was then reduced to succinic acid. More recently an enzyme, oxaloacetic carboxylase, was



found in bacterial and liver extracts; it catalyses reversibly the decarboxylation of oxaloacetic acid (Krampitz, Wood and Werkman, 1943; Krampitz and Werkman, 1941). Thus, carbon dioxide fixation was established as a definite reversible enzymic process (Ochoa, 1946). A similar type of reaction has been identified in the carboxylation of α -ketoglutaric acid to oxalosuccinic acid by oxalosuccinic carboxylase (Ochoa, 1945).

The enzyme systems involved in these fixation reactions have not yet been purified, but they are known to require magnesium or manganese; there is some evidence that, in certain micro-organisms, biotin may be involved (Lardy, Potter and Elvehjem, 1947; Shive and Rogers, 1947). Adenosine triphosphate has also been shown to be required for full activity of an oxaloacetate decarboxylase from liver (Utter and Wood, 1946). The fixation of carbon dioxide in oxaloacetate is an endergonic reaction; adenosine triphosphate may well supply the requisite energy. Phosphorylation probably is also associated with carbon dioxide fixation when pyruvate is formed from acetic acid via acetyl phosphate, the reverse of "phosphoroclastic" splitting of pyruvate referred to on p. 75 (Lipmann and Tuttle, 1945). Like carboxylation of acetate, these carboxylation reactions have their equilibria in favour of carbon dioxide formation, and the keto acids formed must therefore be removed rapidly through the action of pyridine nucleotide dehydrogenases. The keto acids, and their dehydrogenases, play an important part in the oxidative system, known as the *tricarboxylic acid* (or Krebs) cycle.

We have still to account for a method of oxidation of acetic acid, the product of decarboxylation of pyruvate; this is believed to occur by means of the tricarboxylic acid cycle (Krebs, 1943, Wood, 1946). Oxaloacetate condenses with either acetic acid or the acetyl radical derived from decarboxylation of pyruvate (we do not yet know whether acetyl phosphate plays a role in this reaction). A series of successive enzymic reactions, involving an oxidative step, gives rise to α -ketoglutaric acid and carbon dioxide (Fig. 8).

α -Ketoglutaric acid may on further oxidation and decarboxylation through succinic, fumaric and malic acids

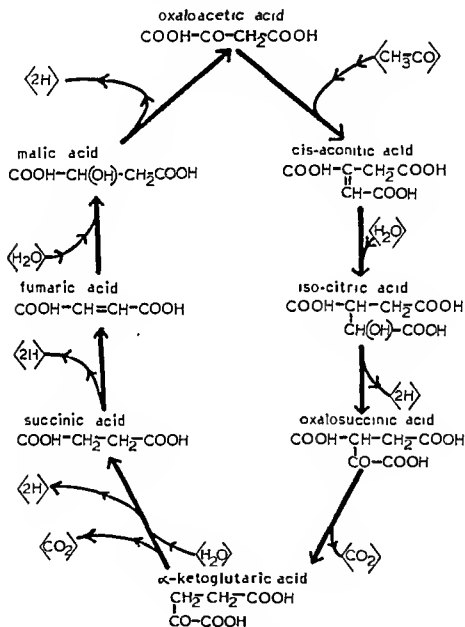


FIG. 8.—The tricarboxylic acid cycle.

regenerate oxaloacetic acid, which can then partake in another cycle. Thus we find that for each complete cycle, one molecule of acetate (derived from one of pyruvate with loss of carbon

dioxide) is completely oxidised to two molecules of carbon dioxide.

Although there is still considerable doubt as to the detailed pathways involved, there is little doubt that some such cycle exists in most cells. Evidence for the cycle originally depended largely on the following facts observed with minced muscle (Krebs, 1943). The conclusions reached can probably be extended also to micro-organisms (Speck, Moulder and Evans, 1946).

(1) All the component acids of the cycle are rapidly metabolised when added to cells under aerobic conditions.

(2) Small amounts of these acids catalyse the oxidation of pyruvate.

(3) Pyruvate oxidation is inhibited by malonate, which is a specific inhibitor for succinic dehydrogenase. In the presence of malonate, succinic acid accumulates when either pyruvate, or fumarate or malate is added. In malaria parasites, acetate is also found to accumulate under these conditions.

Enzymes are known which catalyse all the reactions of the cycle, but few of them have been obtained pure, and some of their coenzymes are still unknown (Lardy and Elvehjem, 1945). Much remains to be done before final proof of the cycle is obtained. Evidence is accumulating that here too phosphorylation is involved, while pyruvate oxidation in the malaria parasite needs diphosphothiamin, both pyridine nucleotides, adenosine triphosphate and manganous ions (Speck, Moulder and Evans, 1946). Evidence for the participation of acetate in the cycle has been provided by the action of fluoroacetate in inhibiting conversion of acetate to citrate (formed enzymically from *iso*-citrate). In tissue slices, none of the oxidative steps in the cycle (i.e. oxidation of *iso*-citric, α -ketoglutaric, succinic or malic acids) were affected by fluoroacetate (Bartlett and Barron, 1947).

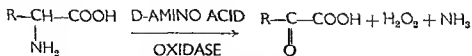
The keto acids taking part in the tricarboxylic acid cycle are acted on by specific pyridine nucleotide dehydrogenases and so can be oxidised through the cytochrome system. Succinic

acid is oxidised to malic acid by succinic dehydrogenase, an enzyme which has not yet been purified and does not fit into any known group of enzymes. It acts through the cytochrome system, but cannot transfer hydrogen to cytochrome through any known pyridine nucleotides or flavoproteins; the intermediary factor is an unknown soluble heat-labile substance (Stoppani, 1947).

The tricarboxylic acid cycle may seem to be over-complicated for the oxidation of a small molecule such as acetic acid. However, the cycle establishes a link between carbohydrate and amino acid metabolism which illustrates well the close integration between degradation and synthesis in the overall metabolic processes of the cell. Every step is essentially reversible, and this reversed cycle provides a means for the reductive fixation of carbon dioxide with ultimate production of pyruvate from which a variety of metabolites may be synthesised (Fig. 9).

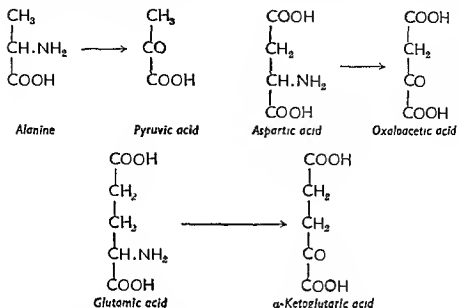
Transamination

We have already mentioned the aëro-dehydrogenase group of enzymes which can transfer hydrogen directly from metabolite to oxygen. The flavoprotein, *D*-amino acid oxidase, is another member of this group; it catalyses the oxidative deamination of *D*-amino acids to α -keto acids, with formation of hydrogen peroxide and ammonia (Warburg and Christian, 1938).



Flavoproteins are known which specifically deaminate certain natural *L*-amino acids in the same way (Blanchard, Green, Nocito and Ratner, 1945). Three of the keto acids whose formation we have traced in carbohydrate metabolism can be formed by this type of reaction. Alanine yields pyruvic acid, aspartic acid yields oxaloacetic acid, while glutamic acid yields α -ketoglutaric acid. Six other commonly occurring

amino acids are known to yield one or other of these α -keto acids indirectly on oxidation.



The reverse process, amination of α -keto acids, does not appear to occur directly, but has been found to take place by a transamination reaction. Enzymes known as *transaminases* catalyse the transfer of an amino group between certain α -keto acids and amino acids (Herbst, 1944).

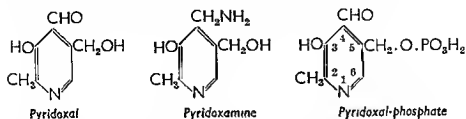


The most completely understood of known transaminations are those involving glutamic acid and oxaloacetic or pyruvic acids. There is no reason to believe that transfer mechanisms



will not be found involving other simple amino acids. Transaminases have been purified to some extent, and are known

to require pyridoxal (vitamin B₆) or its phosphate for activity (Lichstein, Gunsalus and Umbreit, 1945; Umbreit, O'Kane and Gunsalus, 1946; Schlenk and Fischer, 1947; O'Kane and Gunsalus, 1947). The aldehyde radical in pyridoxal is known to be easily and reversibly exchanged for an amino group; pyridoxal may therefore act as a coenzyme for transamination by transporting amino groups.



There has been disagreement as to the position of the phosphate residue in pyridoxal phosphate. Pyridoxal-acetal-phosphate, in which the phosphate is attached to the phenolic hydroxyl at position 3, was found to have limited coenzyme activity in amino acid decarboxylation (p. 135) and no activity as a co-transaminase (Karrer and Viscontini, 1947 *a, b* and *c*). The alternative position of the phosphate on the alcoholic hydroxyl group at position 5 is more probable, since a compound of this structure had high co-decarboxylase activity and was also active as a co-transaminase (Gunsalus and Umbreit, 1947).

POLYSACCHARIDE

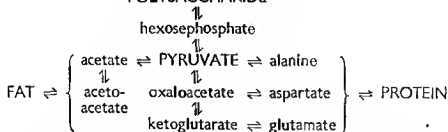


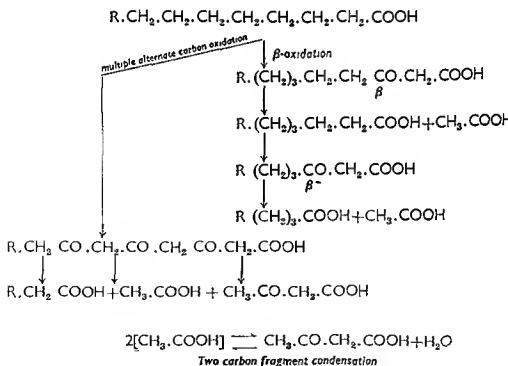
FIG. 9.—Relation between carbohydrate, amino acid and fat metabolism.

The connection between amino acid and carbohydrate metabolism now becomes obvious (Kritzman, 1947; review, Stotz, 1945). Once again pyruvate occupies a key position, and the reason for its participation in the tricarboxylic acid cycle becomes more evident. We can trace a mechanism for formation of simple amino acids from the products of

carbohydrate breakdown or carbon dioxide fixation. This mechanism may be represented diagrammatically as in Fig. 9.

Fat metabolism

Relatively little is known of the nature of fats synthesised by micro-organisms, or of the degradative pathways followed in their utilisation, but the general trend of comparative biochemistry is to find close similarities between metabolic pathways in higher forms of life and in micro-organisms. Fatty acids are believed to be metabolised in animal cells by oxidation at alternate carbon atoms, starting with the β -carbon, with formation of 2 or 4 carbon fragments; the possibility of some ω -oxidation cannot be excluded. The two carbon fragments can be acetate or acetyl phosphate; the four carbon fragments appear as acetoacetate, which can also be



formed by condensation of a pair of two carbon fragments. β -Oxidation may proceed either by a series of discrete steps, or by multiple alternate-carbon oxidation in which numerous

two or four carbon fragments are produced simultaneously (Buchanan, Sakami and Gurin, 1947; Breusch and Ulusoy, 1947; see also review by Stadie, 1945).

The use of labelled carbon has shown that fatty acid metabolism is a reversible process in which acetate, adenosine triphosphate and the tricarboxylic acid cycle all play important parts (review, Wood, 1946). The participation of adenosine triphosphate suggests that phosphorylation may occur (Lehninger, 1945). Fatty acid metabolism in the presence of malonate leads to accumulation of acetoacetate and isocitrate; as malonate inhibits one step in the tricarboxylic acid cycle, this is further evidence for participation by the cycle in fat oxidation (Breusch, 1943; Lehninger, 1946 *a* and *b*; Floyd, Medes and Weinhouse, 1947).

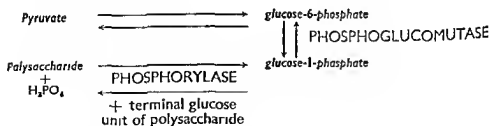
In bacteria the early results of Stephenson and Whetbam (1922) indicated that the amount of lipid synthesised by the Timothy grass bacillus was influenced by the composition of the medium and was greatly increased in the presence of acetate. The conversion during bacterial fermentation of "labelled" acetate containing isotopic carbon to butyric and caproic acids has been demonstrated (Wood, Brown and Werkman, 1945; Barker, Kamen and Bornstein, 1945). The enzymes of all these conversions have yet to be purified, but there seems good reason to believe that in micro-organisms the tricarboxylic acid cycle provides a mechanism, not only for the oxidation of acetate, but also for the integration of carbohydrate, fat and amino acid metabolism.

Carbohydrate synthesis

Carbohydrate breakdown by the living cell is a metabolic process which is to some extent understood. Much remains to be elucidated, particularly with regard to aerobic respiration, but the sequence of enzyme-catalysed reactions from the phosphorylation of hexose to the production of pyruvic acid has been fully verified and even largely reconstructed with pure enzymes under artificial conditions. Such experiments, however, only show that postulated reactions are possible; they cannot show their relative importance or reproduce the

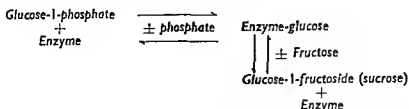
directive influences under which they operate in the living cell. All the steps in the anaerobic breakdown of carbohydrate to pyruvate are reversible, so that the same enzyme systems may either degrade or synthesise a particular substrate according to local cellular conditions (Lardy and Ziegler, 1945).

The aim of synthetic processes is either to form essential cell structures and enzymes, or to store surplus metabolites for future use. The water-solubility of glucose and the high osmotic pressure of its solutions makes it unsuitable as a form of carbohydrate store; therefore, reversal of the phosphorylative breakdown of glucose or any of its intermediates often leads to formation of polysaccharides. During the synthetic process, glucose-6-phosphate is converted by a metalloprotein enzyme, phosphoglucumutase, to glucose-1-phosphate which under the influence of a phosphorylase polymerises to a polysaccharide, the nature of which depends upon the particular phosphorylase and on the nature of the polysaccharide already present in the cell. A crystalline phosphorylase has been isolated from muscle by Green and Cori (1943), and its action has been shown to be the exchange of the phosphate radical of glucosyl-1-phosphate for the terminal glucosyl unit of the polysaccharide already present. The scheme for carbohydrate synthesis from pyruvate may be represented as follows:—

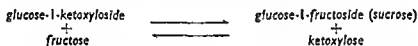


The synthesis of sucrose by *Pseudomonas saccharophila* has been shown to occur through the action of the enzyme sucrose phosphorylase (Hassid, Doudoroff and Barker, 1947; Doudoroff, Barker and Hassid, 1947; Doudoroff, Hassid and Barker, 1947). The primary reaction consists of a combination of glucose phosphate with the enzyme, followed

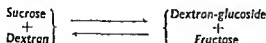
by liberation of phosphate, after which glucose combines with fructose :—



The overall reaction is in effect a transfer of glucose, and since it is reversible, the acceptor may be either a phosphate or a fructose radical. The transfer reaction may, in fact, proceed in the absence of a phosphorylated intermediate with an extraordinary variety of acceptors other than phosphate. For example, many ketose sugars and even certain aldoses will accept glucose, with the result that interconversion of disaccharides may be effected, as may be illustrated by the production of sucrose from glucosidoketoxylside.



The synthesis or degradation of dextran (a glucosan) is accomplished by an enzyme from *Leuconostoc mesenteroides* without addition of phosphate, and no phosphorylated intermediates can be isolated (Cori *et al.*, 1945). The reaction probably involves exchange of one glucosidic linkage for another. The dextran produced *in vitro* by the isolated



enzyme was identical immunologically with that found in the living organism (Hehre, 1943). There is evidence that levans are produced by a similar mechanism.

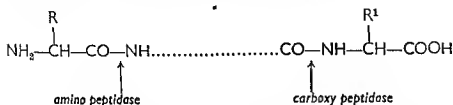
Protein synthesis

Our knowledge of carbohydrate synthesis is based on the reversibility of the enzyme systems taking part in carbohydrate breakdown. Unfortunately, the same cannot be said about

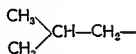
protein synthesis, about which we know practically nothing. Proteins possess a high degree of specificity, each species building its own characteristic pattern; even in the same cell, the number of different proteins must be large to account for the multifarious enzymes present. Enzymes are in addition species specific, as is shown by the immunological properties of catalase and trypsin from different species (Campbell and Fourn, 1939; Northrop, 1939). Different coenzymes are often required by the same enzyme isolated from different organisms; thus, enzymes concerned with pyruvic acid utilisation appear to require either magnesium or manganese as one of their co-factors when isolated from bacteria, but use manganese if they are of animal origin. There is some evidence that the pyridine nucleotide required by malic and glutamic dehydrogenases varies with the source of enzyme (Schlenk, 1945), but this cannot be confirmed until the enzymes in question are purified. The pH for maximum activity of enzymes also varies with the source.

This high degree of specificity among individual proteins points to a similar specificity in the enzyme systems responsible for their synthesis. At present, due to lack of knowledge and to the complexity of the problem, our investigations on specificity are limited to the action of the numerous proteolytic enzymes which degrade proteins and polypeptides. These enzymes, which all hydrolyse the peptide bond, may be divided into two main groups, according to their site of attack (Bergmann, 1942). One group acts only on terminal peptide bonds and can be classed as "exopeptidases," while the second group, the "endopeptidases," are capable of attacking centrally-located peptide bonds and, to a lesser extent, the terminal bonds as well. The older terminology, still in use, refers to these groups as peptidases and proteinases respectively. Within these groups, there are considerable differences in specificity between individual enzymes; the hydrolysis of a given peptide link by a given enzyme appears to be determined largely by the nature of adjacent and nearby amino acids and of the end groups. For example, exopeptidases are subdivided into aminopeptidases and carboxypeptidases, the

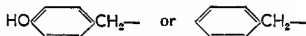
peptide group which is split being adjacent to either a free amino group or a free carboxy group respectively.



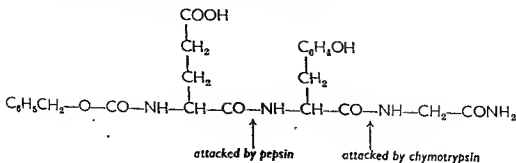
As well as showing this broad specificity, the individual peptidases also require certain groups in the side chain attached to the carbon atom adjacent to the peptide bond. For example, certain amino peptidases will only split a bond in which R is represented by



i.e. the terminal amino acid is leucine, while some carboxy peptidases are known for which R must be



that is tyrosine or phenylalanine are the terminal amino acids split. In the same way, the endopeptidases require certain side groups adjacent to the peptide link, and the specific amino acid thus involved is attacked either through its carboxy or its amino group. This is well illustrated by the action on the same synthetic substrate (carbobenzoxy-L-glutamyl-L-tyrosyl-glycineamide) of pepsin and chymotrypsin, both of which attack a peptide link adjacent to an aromatic amino acid (Bergmann and Fruton, 1941).

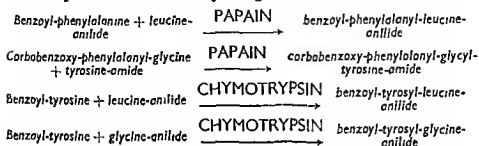


A considerable degree of optical specificity is shown by some proteases and peptidases, so that peptides containing *d*-amino acids in certain positions are not hydrolysed (Bergmann and Fruton, 1941; Stahmann, Fruton and Bergmann, 1946). On the other hand, peptidases are known which hydrolyse peptides containing *d*- as well as *l*-amino acids. Usually the *l*- form is hydrolysed faster than the *d*- form, but some bacterial peptidase preparations split the two forms at approximately equal rates (Berger, Johnson and Baumann, 1941). There is evidence that hydrolysis of *d*-amino acid peptides may be due to an enzyme different from that hydrolysing the natural isomers (Maschmann, 1942, 1943); proof must await actual separation of both enzymes. An alternative suggestion has been made that the same enzyme is involved, but that optical specificity is changed by the presence of certain metals or reducing agents (Bayerle and Borger, 1942; Bayerle and Reiffert, 1942).

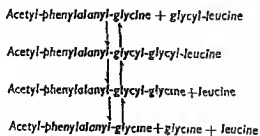
The part played by proteolytic enzymes in protein synthesis is largely conjectural. We are not yet able to assess to what extent, if any, the reversal of proteolytic hydrolysis is responsible for the synthesis of peptide bonds. As Bergmann and Fruton (1944) point out, "perhaps the strongest reason for believing that the enzyme-catalysed condensation of amino acids represents the most probable metabolic course of protein synthesis is the fact that the proteolytic enzymes, by virtue of their sharp specificity, are the only known biocatalysts which could direct, precisely and reproducibly, the complex sequence of successive peptide syntheses required for the formation of a protein."

The enzymic hydrolysis of a peptide bond is, like other enzymic processes, an equilibrium process, but equilibrium is overwhelmingly in favour of hydrolysis. Therefore, the synthesis of a peptide can only occur when the product of reaction is rapidly removed, as is possible in the cell where coupled reaction sequences occur. The *in-vitro* enzymic synthesis of peptides has been achieved by Behrens and Bergmann (1939), using derivatives of amino acids which gave insoluble peptides. For example, the action of papain on a mixture of

benzoyl-leucine and leucine-anilide formed benzoyl-leucyl-leucine-anilide, which is so insoluble in water that a saturated solution is always at a lower concentration than the equilibrium concentration. As a result, the dipeptide was continually removed from solution by crystallisation and the reaction proceeded in the direction of synthesis. Other examples of similar syntheses achieved by Bergmann are as follows:—



The synthesis of a peptide bond requires the provision of a considerable amount of energy (about 3 kg. cal./mol.). From our knowledge of such reactions, we may postulate that this energy may be provided by coupled reactions. A synthesis of a polypeptide coupled with hydrolysis of another peptide has been demonstrated *in vitro* by Bergmann through the action of the enzyme papain on the peptides acetyl-*dl*-phenylalanyl-glycine and glycyl-*l*-leucine. Although neither of the peptides is hydrolysed by the enzyme, an equilibrium is soon set up in solution, with formation of a very small amount of acetyl-*dl*-phenylalanyl-glycyl-glycyl-leucine. This tetrapeptide is at once hydrolysed in two successive steps in which first leucine, and then glycine, is split. The equilibrium is thus upset and further tetrapeptide is synthesised and in turn hydrolysed until all the glycyl-leucine is used up by the synthetic reaction.



The nett result is hydrolysis of glycyl-leucine without change of the acetyl peptide. The existence of such a type of reaction

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Conclusion

It should be evident from this brief outline that the whole process of cellular metabolism is a closely woven, interlocking and interdependent series of enzymic reactions. Disturbance of any one enzymic reaction by introduction of a poison or drug will extend far beyond that single reaction ; if the cell survives, there will occur an overall adjustment in enzymic balance which may become evident either in some fermentative change, in altered demand for foodstuff, in a changed rate of growth or in altered response to further contact with drugs.

Since whole groups of enzymes possess certain common characters, such as a common prosthetic group or coenzyme, it is probable that a drug will affect not a single enzyme but a whole group of related enzymes, some more, others less, essential to life. The problem of reducing drug action to interference with any single enzyme is therefore immense, and the study of intermediary metabolism is likely for the present to do more towards suggesting new types of drugs than towards solving the problem of the mode of action of known drugs.

suggests that in the cell, peptide synthesis and breakdown may be interconnected processes, influenced by the presence of other peptides or proteins.

Speculation enables us to envisage many other coupled reactions which may provide energy for peptide synthesis. Energy transfer might occur through phosphorylation, as in carbohydrate metabolism; the carboxyl or amino group of amino acids, if phosphorylated, would be energy-rich, and could thus couple with another amino acid with liberation of free phosphate. Energy may also be transferred from oxidation-reduction systems in other ways as yet unknown. The possible relation of peptide synthesis to energy supplied through the phosphate bond is suggested by the discovery of two enzymes which catalyse formation of the $-\text{CONH}-$ bond, both of which require adenosine triphosphate and magnesium. One enzyme from rat liver and kidney synthesises a peptide bond between *p*-aminobenzoic acid and glycine (Cohen and McGilvery, 1947); the other, found in sheep brain and *Staph. aureus*, catalyses the formation of glutamine from glutamic acid (Elliott, 1948; Elliott and Gale, 1948).

An alternative method of peptide synthesis has been suggested, namely coupling of a keto acid, e.g. pyruvic acid, with one or two molecules of an amino acid amide with intermediate formation of dehydroamino acid peptides or di(acyl-amino)-propionic acid peptides (Bergmann and Fruton, 1944; Gonçalves and Greenstein, 1948).

The synthetic route for formation of the nucleic acid moiety of nucleoproteins is also largely unknown. There is evidence that the first step, nucleoside formation, involves a phosphate exchange as in polysaccharide synthesis, since the synthesis is known to occur by the action of a nucleosidase enzyme on ribose-1-phosphate and purine (Cori, Hassid, Doudoroff and Kalckar, 1945; Kalckar, 1945, 1946, 1947). In view of this phosphorylative step, Kalckar suggested that the enzyme be known as a nucleosidase phosphorylase.



of synthesis by the cell was so slow as to be insignificant ; (2) as a growth stimulant, when its rate of synthesis was somewhat faster but still slow enough to be a limiting factor ; or (3) as a substance not required at all for nutrition because the cell could synthesise it so fast that it was not a limiting factor in growth."

Let us consider a specific example. Certain strains of *Escherichia coli* can grow on a medium containing only inorganic salts, ammonia and glucose, and must therefore be capable of synthesising all the nitrogenous constituents of the cell. Some strains of *Eberthella typhosa* cannot grow in this medium unless tryptophan is added. The proteins of both organisms contain tryptophan, and we can conclude that *E. coli* synthesises tryptophan, whereas *Eb. typhosa* during its parasitic existence has found it preferable to derive its tryptophan from the host tissues. Tryptophan occurs as an essential intermediate in the metabolism of both organisms, but in culture media it acts as a growth factor for only one of them.

Before proceeding further, it is as well to point out the great variability of the nutritive requirements of a given species of micro-organism. It should be remembered that "the nutritive requirements for a single strain do not necessarily represent those of the species as a whole" (Snell, 1946).

We have already mentioned that the metabolic reactions of heterotrophic micro-organisms do not differ fundamentally from those of animals. Similarity does not imply identity ; the usual amino acids occur in bacterial protein, but for any one species the protein is of characteristic and constant composition (Stokes and Gunness, 1946 *a* and *b* ; Freeland and Gale, 1947). However, owing to the limited data available, it is by no means certain that bacterial protein is made up solely of the amino acids known to occur in animal protein (Blass and Macheboeuf, 1946). As might be expected, the nutritional requirements of micro-organisms resemble in many respects those of higher forms of life. These requirements are simply a reflection of the overall metabolism of the cell and of the

CHAPTER III

ESSENTIAL METABOLITES

DURING growth, catabolism and anabolism proceed simultaneously, and the energy derived from enzyme-catalysed exergonic reactions is utilised in the production of new cellular material. New nucleoproteins, structural proteins, lipoproteins and carbohydrates are formed, new enzymes are elaborated and new prosthetic groups and coenzymes are synthesised for these enzymes. We have seen that some intermediates for synthesis are derived from the products of catabolic reactions; others must be synthesised by specialised routes or obtained preformed from the surrounding environment.

The *autotrophic* group of bacteria are capable of complete synthesis of all cellular materials from carbon dioxide and inorganic salts. Pathogenic organisms are heterotrophic, that is, they require a source of carbon more complex than carbon dioxide. The nitrogen requirements of pathogens vary from the ability to grow on media containing inorganic nitrogen to a complete dependence on preformed amino acids, coenzymes, purines, etc. From the viewpoint of comparative biochemistry, pathogens may be regarded as evolutionary variants which have hit on an easy method of living, obtaining some, at any rate, of their essential organic constituents by leading a parasitic existence and stealing from their hosts. As pointed out by Knight (1945), no clear distinction can be drawn between metabolites "acquired from the environment" and those "synthesised by the cell", since an organism may be able to synthesise an essential cell constituent only very slowly, and during rapid growth must depend on an external source of supply. "Hence a given substance, required as a component of one of the essential metabolic processes might appear in three different roles as a component of the nutrients. It might appear (1) as an 'essential' nutrient when its rate

The growth curve is arbitrarily divided into four phases.

(1) *The lag phase (a to b).*—In the early part of this phase there may be no apparent growth, or even a slight diminution in numbers, but within a short time growth becomes apparent and gradually increases in pace until the beginning of the next phase.

(2) *The logarithmic phase (b to c).*—During this phase, cell division proceeds at a constant and maximal rate. Theoretically, each cell completes a cycle of reproduction with uniform periodicity and doubles itself in unit time. It follows that

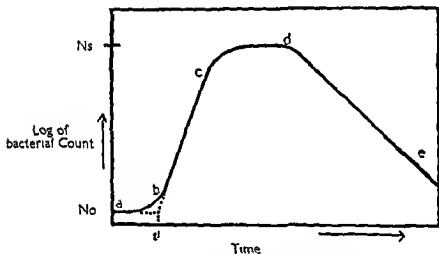


FIG. 10.—Typical bacterial population curve.

successive cell counts plotted logarithmically against time fall on an ascending straight line.

(3) *The stationary phase (c to d).*—Cells gradually cease to multiply at maximal rate until population gain from new division is more or less balanced by death of a similar number of cells.

(4) *Phase of decline (d to e).*—The stationary phase is followed by a period of steady decrease in the number of living organisms, during which reproduction ceases and, after a long time, the culture becomes sterile.

The course of growth is usually characterised by three constants, the length of the lag phase (t^l), determined by extrapolation of the logarithmic growth curve back to the

degree to which parasitism has resulted in reduction of the ability to synthesise essential intermediate metabolites. Animals may be equally well regarded as a form of life ultimately parasitic on the photosynthetic plants, and dependent on these plants for a supply of certain metabolites.

We do not propose to review here all aspects of the subject of bacterial nutrition or to attempt to list the nutritive requirements of bacteria, but rather to indicate firstly, the relationship of nutritive requirements to the enzymic make-up of the cell; secondly, the relation of nutritive requirements to the development of a parasitic form of life; and thirdly, the implications of the nutritional and metabolic viewpoint in the design of chemotherapeutic drugs. It will not be desirable to consider only pathogenic organisms, since in many cases comparison is instructive, while the underlying similarity of intracellular metabolism in pathogen, non-pathogen and host constitutes a major problem in the development of scientific chemotherapy.

Since many diseases are caused by protozoal organisms, it is evident that the subject of protozoal nutrition is as important as that of bacterial nutrition. It will not be dealt with separately here, but where a factor is known to be required by protozoa as well as by bacteria, mention will be made in the text. Many pathogenic protozoa require extremely complex media for cultivation, and some even resist culture outside the host. For example, *Entamoeba histolytica* was even thought to require the presence in the medium of living bacteria, but has now been cultivated in the presence of penicillin-killed bacteria (Jacobs, 1947).

Bacterial growth

The growth of a bacterial population in a suitable medium tends to follow a fairly characteristic pattern which can be conveniently expressed in graphic form by plotting the logarithm of the number of bacteria against time. A typical curve is shown in Fig. 10.

then increases to a constant value when it cannot be eliminated by addition of culture filtrates or by change in medium. This is probably due to a decline in the activity of cell enzymes with age (Gale, 1940; Woods and Trim, 1942). Stephenson (1939) suggests that lag may result from the following causes :—

- (1) Decreased permeability due to the inoculant having remained for some hours in an exhausted medium.
- (2) Decreased enzyme activity due to the same cause.
- (3) Time required for formation of adaptive enzymes.
- (4) Time required for production of highly-reactive molecules in optimum concentration.

The first three causes cannot be eliminated by improvement of the medium and would be most marked in cells coming from old cultures.

The logarithmic phase.—Towards the end of the lag phase, there is an increase in metabolic activity, often associated with an increase in cell size, and followed very soon by cell division which accelerates to a steady maximal rate. During the early part of the logarithmic phase, cells may show a lowered resistance to bactericidal agents, but towards the end of the phase resistance increases again. During the late lag phase and at the beginning of logarithmic growth, cells adapt themselves more rapidly to changes of media than at any other time.

The stationary phase.—During growth in a limited medium, conditions gradually become less favourable due to exhaustion of metabolites, change in pH and accumulation of toxic products (Morel, 1941). The effects of these adverse conditions usually increase from negligibility to vital importance in a short period, and so cause a rapid transition from logarithmic to stationary phase. When the basal medium is deficient, and concentration of any one metabolite is the limiting factor on growth, the maximal cell count becomes directly proportional to the initial concentration of that metabolite in the medium. This enables the concentration of the metabolite to be determined from growth response, growth being measured

value $n = N_0$; the mean generation time or the time required (during logarithmic growth) for the population count to double, and finally the maximal count (N_s), attained during the stationary phase.

The lag phase (cf. Hinshelwood, 1944; Winslow and Walker, 1939). The length, t^l , of the lag phase depends on a number of factors; if the cells of the inoculum are very young, t^l may be considerable, but as the age of the inoculum increases, t^l may fall nearly to zero and then increase again. The stationary period of the lag phase is essentially one of adjustment during which the inoculated cells adapt themselves to new conditions and build up in cell and medium the necessary ingredients for growth. This is well illustrated by the case of *Bacterium lactis aerogenes* which grows on a synthetic medium with ammonium salts as sole source of nitrogen. Young inoculae show a considerable lag period when transferred to a fresh medium; but the lag can be completely removed by addition to the basal medium of a sterile culture-filtrate from a fully-grown culture (Lodge and Hinshelwood, 1943). With older inoculae the lag depends upon the size of the inoculum. These results suggest that for growth *B. lactis aerogenes* requires some diffusible factors which during the lag phase are built up to the necessary threshold concentration. The nature of the growth factors in this case is suggested by the observation that in the presence of amino acids as sources of nitrogen, t^l is no longer affected by inoculum size or by extracts of older cultures.

In general, unfavourable media tend to lengthen the lag phase; thus with *B. lactis aerogenes* on a synthetic medium containing glucose and phosphate buffer, t^l can be increased indefinitely as the concentration of magnesium ions is reduced (Lodge and Hinshelwood, 1939). Growth can be influenced also by insufficient concentrations of carbon dioxide (Walker, 1932; Gladstone, Fildes and Richardson, 1935; Gale, 1945). Aeration of an otherwise suitable medium with carbon dioxide-free air delays growth indefinitely, but reproduction begins immediately carbon dioxide is admitted to the air stream.

As the age of the inoculum increases, t^l falls at first, and

often incomplete, so that an organism may be "trained" to dispense with an amino acid by repeated subculture in a deficient medium. The synthetic mechanisms of exacting organisms can be regarded as having become atrophied or lost through disuse during parasitic life, when the organism could depend on the surrounding host tissue for a supply of amino acids. An organism may sometimes show a gain in growth rate in a rich medium consequent upon loss of synthetic ability (Ryan, 1946; Monod, 1946). In this way a pathogen may find it biologically advantageous to depend upon its host for certain essential metabolites. Such a parasitic strain is termed a "nutritionally exacting" strain. Certain nutritionally exacting strains of *Eberthella typhosa* grew on a simple glucose ammonium salt medium only if a small amount of tryptophan was present (Fildes, Gladstone and Knight, 1933). By serial subculture and gradual reduction in the tryptophan content of the medium, these strains became capable of growth with ammonia as sole source of nitrogen. The trained organisms did not dispense altogether with tryptophan as a constituent of their proteins but had developed the capacity to synthesise the amino acid, since chemical tests showed that tryptophan was present in non-exacting as well as in exacting strains. We do not wish to imply by the term *nutritional training* that slow reduction in tryptophan content of the medium necessarily induced a similar change in all cells of the population examined. When the nutritional requirements of a strain are determined, it is the character of a population rather than of an individual which is being measured. The character of a population may be altered either by selection of individuals from an initially heterogeneous population, or by selection of variants occurring spontaneously during growth of the population, or by induction of variation in some or all of the cells under examination. The question of the ultimate nature of bacterial variation is discussed more fully in Chapter VI.

Although tryptophan was the only amino acid found to be absolutely essential for the growth of certain exacting strains of *Eberthella typhosa*, other amino acids, namely cystine,

by some standard method after sufficient time for the stationary phase to be reached. Fig. 11 represents a typical growth-response curve; it shows the growth (estimated as turbidity) of a strain of *Lactobacillus arabinosus* with varying amounts of tryptophan in an otherwise complete medium (Wright and Skeggs, 1945). Fig. 13 shows normal growth curves for varying amounts of metabolite.

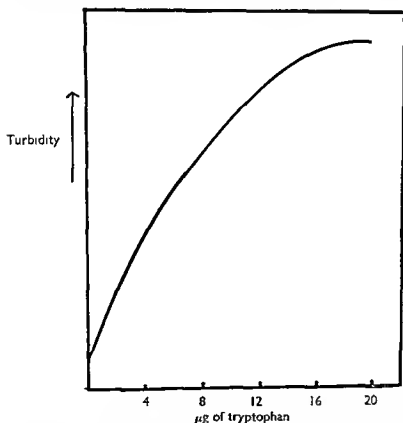


FIG. 11.—Growth response of *Lactobacillus arabinosus* to addition of tryptophan to a deficient medium after 24 hours growth. (Wright and Skeggs, 1945.)

Amino acids as essential metabolites

As noted already, some organisms such as *Escherichia coli*, *Pseudomonas pyocyanea* and Friedlander's bacillus (*Kl. pneumoniae*) can utilise ammonia as sole source of nitrogen; they are thus able to synthesise all their amino acids. Bacteria with more exacting nutritional requirements have lost the capacity to synthesise certain amino acids; but this loss is

form. Some of the more exacting strains required tryptophan, cystine, leucine, valine, proline, glycine, aspartic acid, phenylalanine, arginine, histidine and methionine for full growth. Training to maximum growth in the absence of any one or all of these amino acids, with the exception of cystine, was possible, but the ease of adaptation varied both with the strain and with the amino acid. Training of a strain to become independent of one amino acid often resulted in a simultaneous reduction in its dependence on other amino acids; in other cases training to dispense with an amino acid, for example leucine, could only be accomplished readily if other amino acids were present. These results suggest a certain interdependence between the enzymic mechanisms concerned with amino acid synthesis in the cell. *Streptococci* have even more complex amino acid requirements than *Staph. aureus*, but here again there exist in the laboratory more and less exacting strains, and a certain amount of training is possible. By omitting each of nineteen amino acids in turn from the growth medium, Woolley (1941) was able to show that for a strain of *Strep. haemolyticus*, glutamic acid and tryptophan were absolutely indispensable, but both together were unable to support growth as the only source of organic nitrogen. Before growth would take place, all the following amino acids had also to be present: isoleucine, lysine, arginine, cystine and tyrosine. A full account of the amino acid requirements of various lactic acid bacteria used in quantitative assay of amino acids has been given by Dunn, Shankman, Camien and Block (1947).

The very rapid change which can take place in the nutritional requirements of a pathogenic organism is well illustrated by a study of the glutamine requirements of the "Richards" strain of *Strep. haemolyticus* (McIlwain, Fildes, Gladstone and Knight, 1939; Fildes and Gladstone, 1939). The test organism had to be maintained by repeated mouse-passage, since, after a few sub-cultures on agar, the organism became independent of added glutamine. With the untrained organism from fresh blood, a glutamine concentration of 2.5×10^{-6} M. was sufficient to allow full growth; with

leucine, lysine, tyrosine and histidine had growth-promoting effects when added to a basal medium already containing tryptophan. This type of result, which is common to many studies of the nutritive requirements of micro-organisms, can be taken to indicate that although the exacting strain is capable of synthesising these other amino acids, it cannot carry out the synthesis sufficiently rapidly to meet all its requirements for maximal growth. When one growth factor is supplied, the need for another may become apparent simply because the potential rate of growth is now much greater. The limitation imposed by failure to synthesise one metabolite sufficiently rapidly is overcome by drawing on the medium for a supply of that metabolite, the whole metabolic rate is transformed to a higher plane, and the cellular requirements for every metabolite are stepped up so that another enzymic reaction becomes the limiting factor in the synthesis of new cellular material.

Some exacting strains of *Eberthella typhosa* show absolute growth requirements for amino acids other than tryptophan, such as arginine, glutamic acid or lysine. The amino acid requirements of a given strain can vary with the form of carbohydrate present in the medium (Burrows, 1942). The adaptive capacity of pathogens may be so great that, when first isolated from the host, their amino acid requirements are very much more complex than after one or two subcultures in simple media (McIlwain, Fildes, Gladstone and Knight, 1939). The capacity for adaptation may even be such that it is difficult to estimate the growth requirements of pathogenic organisms as they exist in the host. A chemotherapeutic drug may act by interfering with the utilisation of a metabolite, but if a pathogen is capable of adapting itself to dispense with that metabolite, or to synthesise sufficient for growth even in the presence of drug, then resistance to the drug may develop so rapidly as to make the drug useless as a chemotherapeutic remedy.

The amino acid requirements of *Staph. aureus* have been studied by Gladstone (1937). Strains were found to differ in their requirements and were easily trained to a less exacting

to an essential metabolite is shown for comparison). When grown on a medium containing the minimal concentration of tryptophan, the organism synthesises more tryptophan and the function of the tryptophan initially added would seem to be similar to that of glutamine in the "Richards" streptococcus.

This shortening of the growth lag by tryptophan should be compared with a similar reduction in lag obtained by Lodge and Hinshelwood (1943) by addition of a cell-free

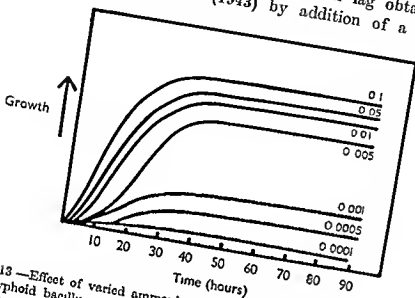


FIG. 13.—Effect of varied ammonium chloride concentration on growth of typhoid bacillus in glucoso-salt medium. Figures on curves represent percentage NH_4Cl in medium. (Burrows, 1939a.)

filtrate of an old culture to a young culture which normally had a long lag period.

An investigation has been carried out on the synthesis of tryptophan by a strain of *Lactobacillus arabinosus* which had been trained to grow in the absence of this amino acid (Wright and Skeggs, 1945). The strain responded to the presence of tryptophan in the medium in a curious manner. The amount of tryptophan synthesised was inversely proportional to the amount present in the medium. Possibly the synthesis of tryptophan depends on an adaptive enzyme (see Chapter VI) which is only produced in direct proportion to the immediate tryptophan demand, or, alternatively, tryptophan added to

smaller concentrations no growth occurred and with larger concentrations there was no augmentation of the growth rate. This "all-or-none" effect is unusual, for the response to addition of a growth factor is usually, within limits, proportional to the amount of factor added. With the exacting "Richards" strain of *Strep. hæmolyticus*, evidently preformed glutamine is essential only for the initiation of multiplication; once growth is started by a minimal amount of glutamine, more glutamine can be synthesised from other constituents of the medium. Other organisms, such as

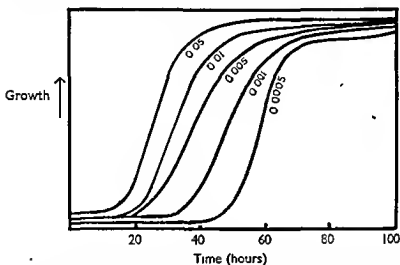


FIG. 12.—Effect of varied tryptophan concentration on the growth of typhoid bacillus in glucose-salt medium. Figures on curves represent percentage tryptophan in medium. (Burrows, 1939a.)

Lactobacillus casei, respond quite differently to glutamiae, their growth rate showing proportionality to the amount of glutamine added to the medium.

A somewhat similar "all-or-none" response to tryptophan has been obtained with the typhoid bacillus (Burrows, 1939 a, b). Provided a minimum amount of tryptophan is added to the medium (about 0.0005 per cent.), increasing amounts of tryptophan have no effect on the growth rate as judged by the slope of the growth curve or on the total population attained, but do reduce the time lag before growth begins (see Fig. 12; also Fig. 13 where a normal growth response

said to be required by *Lactobacillus casei* (Scott, Norris and Heuser, 1946, 1947).

Where stimulation of growth by an amino acid can be shown, the assumption is reasonable that the added amino acid plays an important part in metabolism of the organism in question. The non-essential amino acids, when present in the medium, are often deaminated or decarboxylated and then used as a source of energy and nitrogen (Stokes and Larsen, 1945). The nature of bacterial protein may be independent of the amino acid composition of the medium (Camien, Salle and Dunn, 1945; Freeland and Gale, 1947), while proteins of organisms grown in the absence of non-essential amino acids can be shown to contain those amino acids. Micro-organisms must therefore be capable of synthesising non-essential amino acids either from other constituents of the nutrient medium or from the intermediates of carbohydrate or fat metabolism. A more detailed study of the growth-promoting effects of various amino acids and their precursors can indicate the pathways for some of these syntheses.

Synthesis of tryptophan

As already mentioned, an exacting strain of *Eberthella typhosa* will not grow on a simple salt glucose medium but grows readily if tryptophan is added to the medium. Tryptophan as a growth stimulant can be replaced by indole (Fildes, 1940b). The organism is apparently incapable of synthesising indole, but, if presented with indole, can convert it to tryptophan. Indole was also found to be a growth factor for *Corynebacterium diphtheriae* in a tryptophan-free medium. Some strains of staphylococcus were found to be capable of the conversion of indole to tryptophan whereas other strains required preformed tryptophan. Such results suggest that indole may be an intermediate in the biological synthesis of tryptophan. A further extension of the metabolic pathway is indicated by the capacity of anthranilic acid to act as a growth factor for some strains of lactic acid bacteria in place of either indole or tryptophan (Snell, 1943). It is therefore probable

the medium may inhibit intracellular tryptophan synthesis by a mass-action effect.

These few cases should suffice to indicate the variability of microbial response to growth factors and to exemplify the underlying biochemical similarity in the amino acid requirements of bacterium and animal. Rose (1938) has listed twenty-one amino acids which are normal constituents of dietary proteins. All these can be utilised by the rat, but only ten are essential. Of the ten essential amino acids (see Table 3), nine are absolutely essential; the tenth, arginine, can be synthesised by the rat, but not at a sufficiently rapid rate to meet the needs for normal growth.

TABLE 3

Amino acids in the nutrition of the rat (Rose, 1938)

Essential Amino Acids	Non-Essential Amino Acids
Lysine	Glycine
Tryptophan	Alanine
Histidine	Serine
Phenylalanine	Aspartic acid
Leucine	Glutamic acid
Isoleucine	Proline
Threonine	Hydroxyproline
Methionine *	Citrulline
Valine	Tyrosine
(Arginine)	Cystine
	Asparagine

* Can be replaced by mixture of homocystine and choline.

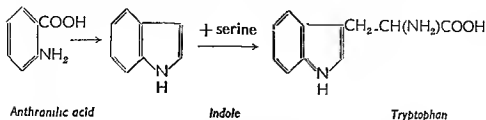
The majority of these twenty-one amino acids have been shown to have growth-promoting properties for some type of micro-organism (Porter, 1946). The amino acid requirements of micro-organisms are not invariably satisfied by a mixture of all the known free amino acids. A low molecular weight polypeptide, known as strepogenin, which can be liberated from proteins, has been found to have growth-promoting properties for bacteria in an otherwise complete synthetic medium (Sprince and Woolley, 1944, 1945). Strepogenin may be related to the peptide seryl-glycyl-glutamic acid which showed limited strepogenin activity (Woolley, 1946b). A heat-stable factor associated with certain proteins is also

in that synthesis. After exposure to X-rays, strains of *Neurospora* were isolated which could not grow on the original simple medium and required the addition of tryptophan or one of its precursors. One strain could not synthesise anthranilic acid but could, if provided with anthranilic acid, grow and synthesise tryptophan. Another mutant could not convert anthranilic acid to tryptophan but could utilise indole. The strain which could form tryptophan from indole but not from anthranilic acid actually produced anthranilic acid, but the next stage in the synthesis was blocked because of lack of the specific enzyme.

Participation of serine in the synthesis was also demonstrated. Indole was only slowly utilised by a growing culture in the absence of serine, but addition of serine caused an increase in the rate of production of tryptophan which was proportional to the amount of serine added. Other theoretically-possible intermediates were completely inactive. A cell-free enzyme requiring pyridoxal phosphate as coenzyme was prepared from *Neurospora* and found to be capable of synthesising tryptophan from indole and serine (Umbreit, Wood and Gunsalus, 1946). The well-known degradation of tryptophan to indole by *Escherichia coli* (Fildes, 1938) was first assumed to be the reverse of the synthetic process (Tatum and Bonner, 1944). Evidence has now accumulated that argument by analogy was misleading. A cell-free tryptophanase enzyme has been isolated from *E. coli* which catalyses the reaction: tryptophan \rightarrow indole + pyruvic acid + ammonia. The enzyme can be resolved into an inactive apo-enzyme and its coenzyme, pyridoxal phosphate. Apparently, serine is not an intermediate in this process, since the purified enzyme did not deaminate serine (Wood, Gunsalus and Umbreit, 1947).

Deductions as to fundamental routes for the biosyntheses of amino acids and other essential metabolites made from studies with X-ray mutants of moulds are thus useful pointers to the metabolic routes followed in other micro-organisms, but are not necessarily applicable to all micro-organisms and should be regarded mainly as a guide to more direct investigation. Fungi, like pathogenic bacteria, often show

that tryptophan is normally synthesised through indole by cyclisation of anthranilic acid.



This assumption has been strikingly confirmed by several different investigations. That of Fildes (1945) showed that indoleacrylic acid, a growth inhibitor which blocks synthesis of tryptophan from indole, is growth-inhibitory when indole has to be converted to tryptophan but not when tryptophan is already present (see Chapter V for further details). Another type of investigation on tryptophan synthesis has been the study by Tatum and Bonner (1944) of nutritive requirements of X-ray mutants of the mould *Neurospora*.

The normal wild-type strains of *Neurospora* are able to grow on a simple medium containing only inorganic salts, a source of organic carbon, and biotin. After exposure to sublethal doses of X-rays, mutant strains may be isolated which are more exacting in their nutritional requirements than the parent strains. The concept that the specific growth requirements of micro-organisms are a reflection, not of intrinsically different needs, but rather of loss of the capacity to synthesise certain metabolites, has already been mentioned. With the mould *Neurospora* genetic analysis is possible, and the synthesis of essential metabolites has been shown to be gene-controlled, each synthetic deficiency being inherited as if it were associated with the mutation of a single gene (Beadle and Tatum, 1941). Any biosynthesis involves a series of consecutive reactions, each catalysed by a specific enzyme. The production of each enzyme appears to be gene-controlled. Mutation may result in loss of the enzyme essential for any one step in a synthetic series, consequently the number of different mutants affecting a given synthesis is a measure of the minimum number of biochemical steps directly involved

the mode of action of metabolite antagonists. It should be noted that the growth-inhibitory effect of one amino acid is generally dependent upon the failure of a strain to synthesise optimal amounts of another structurally-related amino acid.

Metabolite deficiency and metabolic response

Amino acids are involved in the general protein synthesis of the cell, and so are equally essential for the formation of a vast array of enzymes; consequently, deficiency of any one amino acid is hardly likely to be reflected in a recognisable deficiency of any single enzyme or group of enzymes. A knowledge of the amino acid requirements of micro-organisms only provides information about the nature of the overall metabolism of the cell. Information about the part played by certain enzymes may be obtained by growing micro-organisms in media deficient in a single coenzyme or essential trace metal. The cell may then exhibit a lop-sided metabolism which can provide information, both as to the function of the coenzyme or metal, and also as to the relative importance to the cell of different enzymes with common prosthetic groups or co-enzymes. The nature of the response observed on addition of an essential metabolite to a culture containing suboptimal amounts of that metabolite may also indicate its function in the cell.

Metallic metabolites

In discussion of the individual enzymes of cellular metabolism, attention was drawn to the importance of metals such as iron, zinc, magnesium and manganese as essential constituents of numerous enzyme systems. Relatively little is known about the inorganic salt requirements of bacteria. The earlier literature suggested that no ions other than sodium, potassium, chloride, sulphate and phosphate were necessary for growth, but it is now generally recognised that these conclusions were reached because of the difficulty of freeing a medium of all traces of other ions. Only very rigorous and carefully designed experiments using specially purified materials can give reliable information as to the exact inorganic salt requirements of micro-organisms.

an inability to synthesise essential metabolites, which may be regarded as a naturally-occurring evolutionary loss correlated with gene mutation (see Chapter VI).

Amino acid antagonisms

Bacillus anthracis will grow very well on a glucose-salt medium containing the following seventeen amino acids: aspartic acid, valine, leucine, alanine, glutamic acid, isoleucine, phenylalanine, lysine, glycine, proline, hydroxyproline, tyrosine, arginine, histidine, cystine, methionine and tryptophan. If, however, valine, leucine or isoleucine is added singly to a mixture of amino acids able to support growth without it, growth is prevented (Gladstone, 1939). The toxic effect of leucine may be counteracted by valine, and *vice versa*; the toxic effect of isoleucine is only overcome if both valine and leucine are added. Other antagonisms were found between threonine and serine and between valine and α -aminobutyric acid. Similar types of antagonistic pairs have been noted with other organisms. Glutamine and aspartic acid are antagonistic for *Lactobacillus casei* (Feeney and Strong, 1942); leucine and methionine are antagonistic for *Proteus morgani* (Porter and Meyers, 1945). Possibly these antagonisms arise because of close relationships between the mechanisms for biological synthesis of the antagonistic pairs, the precursor of one amino acid being able to interfere with formation of another. This view is supported by isolation of a "valine-less" (*i.e.* unable to synthesise valine) X-ray mutant strain of *Neurospora crassa* which was found to require both isoleucine and valine in an optimal ratio of 70-80 per cent. valine to 30-20 per cent. isoleucine (Bonner, Tatum and Beadle, 1943; Bonner, 1946). This apparent double requirement of a single mutant is thought to be due to failure of amination of keto-isoleucine to isoleucine with consequent accumulation of keto-isoleucine. The keto acid may specifically inhibit amination of the closely related keto-valine, so preventing synthesis of valine.

These examples of amino acid antagonisms indicate the complexity of the interpretation of nutritional studies, and suggest the difficulties which have to be met in interpreting

the amount of iron present, and the iron content of the cells showed a direct relationship to the concentration of iron in the medium. *Aerobacter indologenes* grown on a medium deficient in iron showed only 5 per cent. of its normal catalase and peroxidase activities. The cytochrome activity, as indicated by cyanide-sensitive aerobic respiration, was normal, but the two weak cytochrome bands visible in normal cells were no longer visible in the iron-deficient organisms. The dehydrogenase activity of the deficient cells was unimpaired except for a loss of formic dehydrogenase and formic hydrogenlyase. It appears that the iron-deficient cells had dispensed with the less essential enzymes dependent on iron, in order to spare the available metal for the more essential cytochrome system. Essentially similar results were obtained with *Aerobacter aerogenes* by Perlman (1945) who utilised cationic exchange resins to free the medium from trace elements.

The nature of glucose metabolism by *Clostridium welchii* depends on the iron content of the medium (Pappenheimer and Shaskan, 1944). As the available iron is reduced, the fermentation changes from a predominantly acetic-butyric acid type, producing large amounts of carbon dioxide and hydrogen, towards a lactic acid type of fermentation which produces little gas. *Cl. welchii* does not possess a cytochrome system but apparently iron plays some essential part in its normal glucose fermentation. Almost complete inhibition of normal glucose fermentation of *Cl. tetani* can be caused by treatment of a washed suspension of normal organisms with α : α' -dipyridyl, a reagent which is known to combine with ionic iron but not with the iron of hæmatin enzymes. Azide, which acts as an inhibitor of hæmatin enzymes, has no inhibitory effect on fermentation (Lerner and Pickett, 1945). Earlier observations by Kubowitz (1934) suggest that iron or another heavy metal is an essential part of some enzyme involved in the acetic-butyric acid type of fermentation of *Clostridium butyricum*. High concentrations of carbon monoxide, which are known to inactivate heavy metal catalysts, diverted the fermentation to the production of lactic acid. The commercial conversion of maize mash to acetone and butyl

The trace element requirements of only a few micro-organisms have been investigated (Young, Begg and Pentz, 1944). Zinc has been almost completely removed from a medium by extraction with a solution of diphenylthiocarbazone in carbon tetrachloride (Feeney, Lightbody and Garibaldi, 1947). The medium, containing less than 0.004 parts per million of zinc, supported slow growth of *Bacillus subtilis* but the antibiotic, subtilin, normally produced by the strain, was no longer synthesised. As the zinc content of the medium was increased, both growth and antibiotic production increased towards normal. The growth of *Corynebacterium diphtheriae* can be greatly slowed by reduction of the iron content of the medium. As the iron content of the medium is raised above the minimal requirement, increased growth is accompanied by increased excretion of diphtheria toxin and of porphyrin. Beyond a critical level of iron there is a rapid fall in yield of toxin and porphyrin, but growth rate continues to increase (Pappenheimer and Hendee, 1947). Simultaneously with the fall in porphyrin excretion there appears, in the cell suspension, the characteristic spectrum of cytochrome *b*. Small amounts of cytochrome *a* have also been reported in *C. diphtheriae*, but no cytochrome *c* (Rawlinson and Hale, 1948). Pappenheimer and Hendee suggest that the cell may be unable, in an iron-deficient medium, to synthesise complete cytochrome *b* but continues to synthesise parts of the molecule which appear in the medium as porphyrin and diphtheria toxin.

Waring and Werkman (1942 *a* and *b*, and 1944) freed media from traces of iron by treating with 8-hydroxyquinoline and extracting the iron-quinoline complex with chloroform. Using these media, they found that *Escherichia coli*, *Aerobacter indologenes* and *Klebsiella pneumoniae* required 0.02 to 0.03 parts per million of iron for growth. *Pseudomonas pyocyanea* unlike these other three organisms which have incomplete cytochrome systems, normally shows a complete 4-banded cytochrome spectrum and high peroxidase and catalase activities; as might be expected, it required three to four times more iron. When the iron content of the medium was suboptimal, growth of all these organisms was proportional to

likely to be of less importance to the cell. This interpretation was supported by reports that *Hæmophilus influenzae* did not require X-factor for growth in the absence of oxygen. A careful study by Gilder and Granick (1947) suggests that this may be only partially true since *H. influenzae* Turner requires a limited supply of hæme even in the complete absence of oxygen.

Lwoff (1933*b*, 1936) found that trypanosomes grown in media containing suboptimal amounts of hæmatin showed a respiratory rate of about one-third normal; the reduced

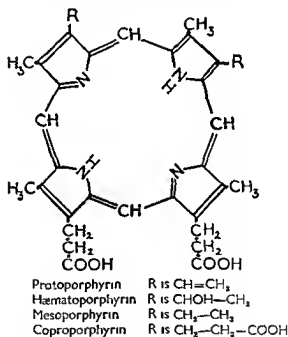


FIG. 14.—Porphyrin skeleton.

respiration was restored to normal by hæmatin, or by protoporphyrin and iron. Although cytochrome alone could not replace hæmatin, in the presence of suboptimal amounts of blood it caused considerable augmentation of growth of trypanosomes.

The loss of synthetic ability of *H. influenzae* lies in a failure to synthesise protoporphyrin, since "X-factor" may be replaced by a mixture of iron and protoporphyrin. Various strains differ in their response to other porphyrins. In some strains iron-mesoporphyrin or mesoporphyrin in low concentration supports growth, in others, the vinyl side-chains (see Fig. 14) are essential and compounds such as coproporphyrin,

alcohol by *Cl. acetobutylicum* is also inhibited by carbon monoxide, but in a continuous stream of carbon monoxide a suitable cell suspension can convert glucose to lactic acid (Simon, 1947).

It is apparent from these few results that much useful information on the enzymic function of trace metals is likely to accumulate as methods are developed for the preparation of metal-free media. It hardly needs to be emphasised that any organic compound capable of forming a stable organo-metallic complex is a potential enzyme inhibitor, and a suitable pattern for chemotherapeutic research.

Organometallic metabolites

A few groups of organisms seem to have lost the capacity to synthesise hæme enzymes from iron. Davis (1917) found that *Hæmophilus influenzae* (Pfeiffer's bacillus) could not grow in peptone broth unless supplied with two additional growth factors, one of which was thermostable and occurred in blood pigments. Thjotta and Avery (1921) suggested the term "X-factor" for the growth substance contained in blood pigments and the term "V-factor" for the other, thermolabile, growth factor present in tissue extracts. Over a period of years, "X-factor" has been shown to be essential for several other species of the genus *Hæmophilus* and for *Bartonella bacilliformis* and *Pasteurella pestis*, also for some protozoa including several trypanosomes and leishmania (Jiménez, 1940; Rao, 1939; Lwoff, 1938). The X-factor was found by A. and M. Lwoff (1933 *a, b*) to be part of the iron-containing pigment of blood; hæmoglobin itself was much less active than the porphyrin pigment hæmatin; other porphyrin pigments such as chlorophyll were inactive, but catalase and plant peroxidase had activity. Lwoff suggests that exacting organisms have lost the capacity to synthesise from simple nutrients the iron-porphyrin enzymes such as cytochrome oxidase, catalase and peroxidase. The iron-porphyrin enzymes are concerned with aerobic metabolism and with the immediate destruction of any hydrogen peroxide formed under aerobic conditions; under anaerobic conditions those enzymes are

is possibly used by the organism as a source of coenzyme I, but adenosine, nicotinamide and nicotinic acid are inactive (Lwoff and Lwoff, 1936, 1937a; Schlenk and Gingrich, 1942; Gingrich and Schlenk, 1944). All micro-organisms which do not require "V-factor" are believed to synthesise it, either from inorganic salts and a carbon source, or from preformed portions of the molecule such as nicotinic acid and adenine. In other words, coenzymes I and II are essential parts of the enzymic structure of all organisms, but there is considerable variation in the ability of different micro-organisms to carry out the various steps of synthesis. A mixture of nicotinamide, *d*-ribose and adenylic acid cannot replace coenzyme I in promoting the

TABLE 4

Relative growth-promoting effects of Nicotinamide and Nicotinic Acid for different bacteria

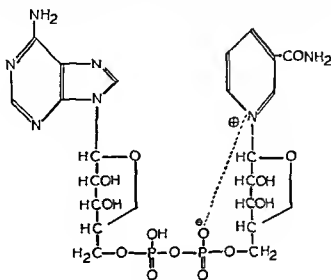
Organism	Ratio of activity of amide/acid
<i>C. diphtheriae</i>	1 : 10
<i>Pr. vulgaris</i>	1 : 1
<i>Staph. aureus</i>	5 : 1
Dysentery bacillus	10 : 1
(certain) <i>Pasteurellae</i>	∞ (acid ineffective)

Koser, Berkman and Dorfman (1941)

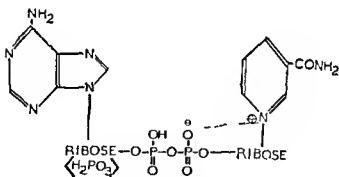
growth of *Hæmophilus influenzae*, but nicotinamide riboside is able to maintain growth. This organism has apparently lost the capacity to link nicotinamide with ribose, but can perform the other steps in the synthesis of the pyridine nucleotides.

Other organisms which fail to synthesise coenzyme from inorganic salts and carbohydrate usually do so because of their inability to synthesise nicotinic acid or nicotinamide. Nicotinic acid can act as a growth factor for various organisms, but different species differ considerably in their ability to convert nicotinic acid to nicotinamide, and hence in their ability to utilise nicotinic acid in place of nicotinamide. This difference is indicated in Table 4, which shows that *Coryne-*

mesoporphyrin and hæmatoporphyrin fail to support growth or even inhibit growth. Simple esterification of the propionic acid side-chains of hæmatin or protoporphyrin may prevent utilisation (Granick and Gilder, 1946; Gilder and Granick, 1947).



Coenzyme I

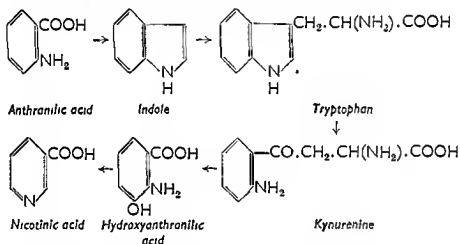


Coenzyme II

Nicotinic acid derivatives

Thjötta and Avery (1921) suggested the name "V-factor" for the thermolabile growth factor contained in tissue extracts and required by *Hæmophilus influenzae*, but were unable to elucidate its nature. It was not until 1936 that the "V-factor" was identified by Lwoff, as di- or possibly triphosphopyridine nucleotide (coenzyme I or II). Coenzyme II is rather less active as a growth factor than coenzyme I and

by mutation. Two of the mutant strains were, however, able to convert tryptophan or kynurenine to nicotinic acid. Two other genetically-distinct "nicotinic acid-less" strains were unable to use tryptophan or kynurenine but, when supplied with minimal quantities of nicotinic acid, accumulated hydroxyanthranilic acid in the medium (Bonner, 1948; Mitchell and Nye, 1948). These results suggest that a biosynthetic route (formulae below) for nicotinic acid synthesis may extend from anthranilic acid, through indole and tryptophan (p. 107) to kynurenine, with some still unrecognised further stages through hydroxyanthranilic acid.

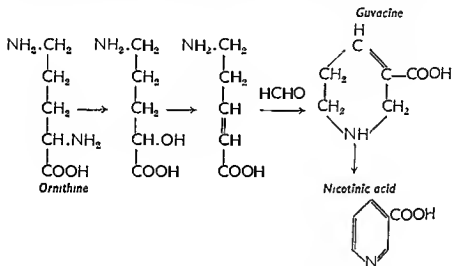


Structural specificity of substituted pyridines

As already indicated, growth requirements are in no way absolute and depend upon the environment in which a test is made, so that it is impossible to classify pyridine derivatives as active, partially active and completely inactive as growth factors. It is possible, however, to take a broader view and to consider pyridine derivatives as potential precursors of essential coenzymes which may or may not, according to the metabolic abilities of a micro-organism, be converted to a form suitable for incorporation into essential coenzymes. An examination of the data collected by various workers on the growth-promoting activity of pyridine derivatives, leads to the general conclusion that unless the pyridine ring is substituted in the 3 position, as in nicotinic acid, it cannot be utilised. The two

nicotinamide may be trained to dispense with it (Koser and Wright, 1943). The trained organisms continue to synthesise "V-factor" and must therefore have developed the capacity to synthesise nicotinamide.










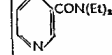
Little is known of the route by which nicotinic acid is synthesised by those organisms which do not require an external source. Ornithine may be deaminated to ω -amino-propylideneacetic acid and cyclised by reaction with formaldehyde to give guvaccine as indicated in the following scheme:—



Guvaccine or hexahydronicotinic acid have been found to replace nicotinamide in the nutrition of *Staph. aureus* and *Proteus vulgaris* (Euler, Högberg, Karrer, Salomon and Ruckstuhl, 1944).

An alternative route for nicotinic acid synthesis has been suggested by a study of "nicotinic acid-less" mutants of *Neurospora*. Genetic analysis of the induced mutants suggested that nicotinic acid synthesis might be blocked at any one of three separate loci. Possible precursors of nicotinic acid, such as pyridine, β -picoline, γ -picoline, piperidine, piperidine-3-carboxylic acid (hexahydronicotinic acid), trigonelline, ornithine, proline, α -amino-*n*-valeric acid and α -amino-*n*-caproic acid were all unable to replace nicotinic acid for growth of the mutant strains and were, therefore, not likely intermediates on the biosynthetic pathway blocked

Pyridine derivatives as growth factors

Substance		Organism			
Name	Formula	<i>Staph. aureus</i>	<i>Shigella dysenteriae</i>	<i>Proteus vulgaris</i>	<i>Lactobacillus arabinosus</i>
Nicotinic acid		+	+	+	+
Nicotinamide		+	+	+	+
Picolinic acid		-	-	-	-
Isonicotinic acid		-	-	±	...
Quinolinic acid		-	+	±	..
Cinchomeronic acid		...	-
α-Picoline		-
β-Picoline		-	-	+	..
Ethyl nicotinate		+	+	+	-
Coramine		-	+	+	...

Adapted from Knight (1945).

isomeric acids, picolinic and isonicotinic, fail to promote growth (Table 6). Introduction of a second substituent into the ring of nicotinic acid usually produces an inactive compound, but some micro-organisms can use pyridine-2:3-dicarboxylic acid, presumably because they are capable of converting the dicarboxylic acid to nicotinic acid. This observation raises an interesting question which cannot be answered until methods are worked out for the complete synthesis of coenzymes I and II. It is not clear whether the inactivity of some compounds is due to the inability of micro-organisms to build them up into a coenzyme-like structure, or is due to a functional failure of a coenzyme built on a slightly different pattern from the normal structure. Where inactivity is confined to a few species of micro-organisms and the same compound can be utilised by other species, the failure is presumably in the initial synthesis of coenzyme. Where all species fail to grow when a nicotinic acid analogue is substituted for nicotinic acid, the failure may be functional; in other words, an enzymically inactive analogue of coenzyme I or II may be synthesised but not utilised. Some of the results of testing pyridine derivatives as growth factors are summarised in Table 6.

Purines and pyrimidines

The ability to synthesise the adenylic acid portion of phosphopyridine nucleotides seems to be less frequently lost in parasitic organisms than the ability to synthesise the nicotinic acid part of the molecule. This difference may be related to the very wide biological importance of adenine and closely related purines. Adenine is not only essential for synthesis of "V-factors," but is also a component of many other enzyme systems, for example the flavin adenine nucleotides; and in the form of adenosine di- or triphosphate, it plays a fundamental role in energy transfer. In addition, adenine and the related purine guanine form an important part of bacterial nucleoprotein (Stahl, Pennel and Huddleston, 1939). It is not surprising therefore that a parasitic organism hesitates for strategic reasons before lowering its tariff barriers

thymine and uracil as components of nucleic acid from *Mycobacterium tuberculosis*. Later Johnson and Brown (1922) reinvestigated the problem and identified thymine and cytosine but could not identify uracil. The nucleic acid from the closely related organism *Mycobacterium phlei* contained, in addition to adenine and guanine, the pyrimidines cytosine and uracil but no thymine (Coghill, 1931). The nucleic acid from *Corynebacterium diphtheriae* contained all three pyrimidines (Coghill and Barnés, 1932). Recent work by Sevag and his colleagues has indicated that the nucleic acid of *Strep. haemolyticus* is a mixture of the desoxyribose and ribose types (Sevag, Smolens and Lackman, 1940; Sevag and Smolens, 1941).

Uracil has been found essential for anaerobic culture of *Staph. aureus* but is probably synthesised by the organism under aerobic conditions (Richardson, 1936). Various exacting strains of lactobacilli respond to thymine and cytosine as well as to uracil (Snell and Mitchell, 1941).

The assumption that micro-organisms requiring pyrimidines build these bases up partly to the nucleic acid form is supported by the nature of the growth response of "pyrimidine-less" X-ray mutants of *Neurospora*. The pyrimidine nucleosides uridine and cytidine and the nucleotides uridylic acid and cytidylic acid were from ten to sixty times as active as the two most active pyrimidines uracil and orotic acid (Loring and Pierce, 1944). Stokes (1944) suggested that folic acid may participate in the synthesis of pyrimidines, since high concentrations of thymine or its nucleoside can replace folic acid in the nutrition of *Streptococcus faecalis*. Other pyrimidines or pyrimidine analogues containing the 5-methyl group can replace thymine, a sulphur analogue of thymine (5-methyl-2-oxy-4-thiopyrimidine) being as active as thymine itself (see Table 7) (Hitchings, Falco and Sherwood, 1945). Purines have been implicated as products of the metabolic system of the cell which requires *p*-aminobenzoic acid, and *p*-aminobenzoic acid is a component of folic acid; in other words, failure to utilise *p*-aminobenzoic acid may result in failure of the whole nucleic acid synthesising system (see Chapter V for further discussion).

and allowing foreign-manufactured adenine to displace the home-made product, even though the imported article may be economically desirable.

A strain of *Strep. haemolyticus* has been found to require both nicotinic acid and adenylic acid or other purine (*i.e.* both portions of coenzymes I and II) at low carbon dioxide pressures (Pappenheimer and Hottle, 1940). Other strains of this organism could not utilise adenine, but grew on xanthine, guanine, hypoxanthine, guanosine or adenosine (Wilson, 1945). Various lactic acid bacteria may also fail to grow under certain conditions in the absence of adenine or guanine (Snell and Mitchell, 1941), but more usually these purines have been found to have growth-stimulating rather than growth-initiating effects (Feeney and Strong, 1942; Snell and Mitchell, 1942). The distinction is perhaps somewhat academic, since a substance which promotes growth under one set of conditions may initiate growth under another. In either case, the nutrient is playing an essential part in cell metabolism.

Purines have been found to be essential metabolites for protozoa and for fungi as well as for bacteria, another indication of the fundamental unity of intermediate metabolic pathways in different types of living cells (Kidder and Dewey, 1945; Robbins and Kavanagh, 1942).

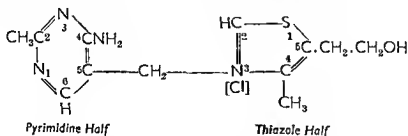
Up to the present, studies on purine-starved organisms have not implicated any particular enzymic systems, but the growth response of deficient "adenine-less" *Neurospora* was greater with coenzyme I than with adenine or adenosine (Pierce and Loring, 1945). Purine deficiency has, however, received relatively little attention as yet, and it is possible that further study will indicate specific enzymic deficiencies in purine-starved cells. Suggestions have been repeatedly made during recent years that purines are concerned with *p*-amino-benzoic acid metabolism and therefore with the mode of action of sulphonamides. This aspect of purine function will be more fully discussed in Chapter V.

So far as we know from the scanty data available, bacterial nucleic acid, like yeast and animal nucleic acid, is built from pyrimidines as well as purines. Levene (1904) identified

component of a number of enzyme systems, particularly those concerned with pyruvate metabolism (p. 73).

From a study of the change in metabolism following addition of thiamin to thiamin-starved *Staph. aureus*, Hills (1938) concluded that anaerobic dismutation of pyruvate to lactate, acetate and carbon dioxide depended on an enzyme system involving thiamin. Later Smyth (1940) extended these results by showing that oxaloacetate could to some extent replace thiamin, suggesting that one of the functions of thiamin may be to catalyse the formation of oxaloacetate from pyruvate and carbon dioxide. When thiamin was added to thiamin-deficient *Propionibacterium pentosaceum* there was a considerable lag period (120 mins.) in the commencement of anaerobic production of carbon dioxide from pyruvate. Addition of diphosphothiamin (co-carboxylase) under similar conditions cut the lag period to thirty minutes. Presumably the thiamin had to be converted to diphosphothiamin before becoming functional in anaerobic pyruvate metabolism (Silverman and Werkman, 1939b). An accumulation of pyruvic acid in aerobic glucose utilisation of thiamin-deficient organisms has been noted; the addition of thiamin to the cells stimulated aerobic but not anaerobic glucose utilisation (Kligler, Grossowicz and Bergner, 1943).

For convenience of discussion the thiamin molecule is regarded as made up of two "halves." The pyrimidine half and the thiazole half, numbered as indicated below.



Micro-organisms can be divided into four groups according to their ability to synthesise thiamin :—

- (1) Those which synthesise thiamin from simpler constituents of the medium.

As more complete information is collected on the metabolism of pyrimidine-starved organisms and on the metabolic effects induced by added pyrimidines, functions additional to those of nucleoprotein synthesis may be allocated to these bases.

TABLE 7
Response of L. casei to various pyrimidines

Substance	Concentration, mg./10 ml.	Effect of Pyrimidine in Various Media. Change of Acid Titre per cent.		
		Unsupplemented	With thymine, 1 µg/ml.	With folic acid, .0014 µg/ml.
Thymine	0.01	+500	0	+20
5-Methyl cytosine	0.1	+200	..	"
5-Methyl isocytosine . . .	0.2	+300	0	+10
5-Methyl-2, 4-diamino-pyrimidine	1.0	+300	-20	+20
5-Methyl-2-thio-4-oxy-pyrimidine	0.05	-30	+10	+10
5-Methyl-2, 4-dithio-pyrimidine	0.25	+20	-25	0
5-Methyl-2-oxy-4-thio-pyrimidine	0.004	+300	+15	0
5-Methyl-2, 4-dioxy-6-amino-pyrimidine	1.0	-10	0	0
5, 6-Dimethyl-2, 4-dioxy-pyrimidine	1.0	0	0	0
2, 5-Dimethyl-4-oxy-pyrimidine	1.0	+30	+10	+10
5-Hydroxy uracil	1.0	-50	-70	-75
5-Amino uracil	1.0	-50	-25	-55
5-Carbamido uracil	1.0	-50	-55	0
5-Chloro uracil	1.0	+45	-93	+20
5-Bromo uracil	0.2	+20	-40	+15
5-Iodo uracil	1.0	0	-40	-20
5-Nitro uracil	0.2	0	-14	-65

From Hitchings, Falco and Sherwood (1945).

The special case of the enzymic function of the "pyrimidine half" of thiamin (vitamin B₁) is treated separately.

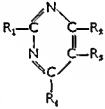
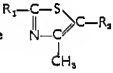
Thiamin (vitamin B₁ or aneurin)

Thiamin is an essential metabolite for bacteria, fungi, protozoa, plants and animals, and has been identified as a

structures be synthesised and utilised? Insufficient information is available to give a definite answer; in this, as in other similar cases, a study of the specificity requirements for coenzyme action in isolated enzyme systems would be instructive. There are indications that in pea roots, at least,

TABLE 8

Effect of structure on availability of pyrimidines and of thiazoles as growth factors for Staph. aureus

Pyrimidines					Thiazoles		
General Structure					General Structure		
							
R ₁	R ₂	R ₃	R ₄	Response	R ₁	R ₂	Response
CH ₃	NH ₂	CH ₃ .NH ₂	H	++++	H	CH ₃ .CH ₂ .OH	++++
CH ₃	NH ₂	CH ₃ .OH	H	++++	H	CH ₃ .CH ₂ .OAc	+++
CH ₃	NH ₂	CH ₃ .NH.CSH	H	++	H	CH ₃ .CHOH.CH ₃	++
CH ₃	OMe	CH ₃ .NH ₂	H	—	H	CH ₃ .CH ₂ .CH ₂ .OH	++
CH ₃	NH ₂	CH ₃ .CONH ₂	H	—	H	—CH=CH ₂	+
CH ₃	OH	CH ₃ .NH ₂	H	—	H	CHOH.CH ₃	—
CH ₃	OH	CH ₃ .OH	H	—	CH ₃	CH ₃ .CH ₂ .OH	—
CH ₃	NH ₂	CH ₃	H	—	OH	CH ₃ .CH ₂ .OAc	—
CH ₃	OH	NH ₂	CH ₃	—	H	CH ₃ .CH ₃	—
CH ₃	OH	H	NH ₂	—	H	CH ₃	—
OH	NH ₂	H	H	—	H	H	—

Some plants and micro-organisms are less exacting and can use some of the compounds not available to *S. aureus* (Knight, 1945). Pyrimidines were tested in presence of excess of the "thiazole half" and vice-versa. (Data from Knight and Mellman, 1938).

thiazole analogues may be functionally active, although thiamin itself is not synthesised; in other words, a functionally-active analogue of thiamin may be synthesised (Bonner and Buchman, 1938).

Table 8 giving the relation of structure to growth response does not indicate fully the extent of the response. In the

- (2) Those which can synthesise thiamin if supplied with one "half" of the molecule.
- (3) Those which can synthesise thiamin only if supplied with both "halves" of the molecule.
- (4) Those which cannot synthesise thiamin even if supplied with both "halves."

These four groups represent successive stages in loss of synthetic ability following upon the adoption of a parasitic existence. It must be remembered that this type of classification is a convenience rather than an actuality, and loss of synthetic ability is a finely-graded process capable of alteration in an altered environment. Certain gonococci may represent a fifth group with even less synthetic ability, since they are unable to utilise thiamin itself but require thiamin pyrophosphate (co-carboxylase) preformed in the medium. Thiamin in this case even inhibits growth by competition with co-carboxylase (Lankford and Skaggs, 1946). Although many strains of micro-organisms have lost the ability to synthesise thiamin, none, so far as is known, has at the same time lost the need for thiamin as a component of its metabolic system.

For growth of *Staph. aureus*, a mixture of the pyrimidine and thiazole "halves" can replace the intact molecule, and the organism must be presumed to possess an enzyme capable of uniting the two parts. Striking confirmation of the necessity of the complete molecule rather than the constituent parts for metabolic function is provided by a "thiamin-less" mutant of *Neurospora* which has been found to be able to synthesise both "halves" but cannot dispense with thiamin because it is unable to join the two together (Tatum and Beadle, 1945; Tatum and Bell, 1946). *Staph. aureus* is capable of utilising some pyrimidines and thiazoles closely related to the natural "halves" of thiamin as is indicated in Table 8. The response of certain protozoa to various pyrimidines and thiazoles is summarised by Lwoff (1947).

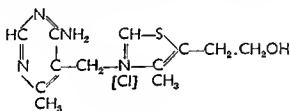
The question naturally arises, does the micro-organism convert all the active analogues of the natural components to a common coenzyme, or can coenzymes of slightly different

metabolite for micro-organisms as well as for more highly organised life. Where intracellular synthesis is inadequate or where synthetic capacity has been lost following upon a period of parasitic life, riboflavin acts as an essential growth factor or growth stimulant until capacity to synthesise the vitamin is recovered. Loss of synthetic capacity has been most frequently reported among hæmolytic streptococci and lactic acid bacteria (Woolley and Hutchings, 1940; Schuman and Farrell, 1941; Snell and Strong, 1939 *a* and *b*). Actual synthesis of riboflavin has been found in various fungi, moulds and bacteria, including *Mycobacterium tuberculosis*, *Staph. aureus*, *Corynebacterium diphtheriæ* and *Clostridium butyricum* (Warburg and Christian, 1933; Boissevain, Drea and Schultz, 1938; Evans, Handley and Happold, 1939; Peterson and Peterson, 1945; see also Knight, 1945). The extent of riboflavin synthesis is much influenced by the composition of the medium (Mayer and Rodbart, 1946).

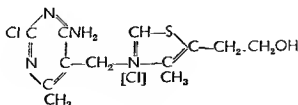
Although the enzymic function of riboflavin is fully recognised, there is little evidence available as yet of impairment of any one specific metabolic capacity in intact riboflavin-starved micro-organisms. This may be related to the tendency shown by the majority of micro-organisms to synthesise riboflavin when transferred to a riboflavin-free medium. Adler and Euler (1934) found that riboflavin stimulated the oxygen uptake of riboflavin-deficient lactic acid bacteria and that the additional oxygen uptake was not inhibited by cyanide, showing that it did not go through the cytochrome system. When *Clostridium acetobutylicum* was grown on an iron-deficient medium, riboflavin synthesis increased, suggesting that riboflavin was taking the place of an enzyme system dependent on iron (Tanner, Vojnovich and van Lanen, 1945; Hickey, 1945).

Nutritional requirements for riboflavin are dependent on the nature of the medium; thus, propionic acid bacteria require riboflavin if grown on a medium with ammonium salts as source of nitrogen, but if grown on an amino acid medium no additional growth factor is required (Wood, Andersen and Werkman, 1938). Some strains of lactic acid bacteria when

presence of the pyrimidine half, the two thiazoles 4-methyl-5- γ -hydroxypropylthiazole and 4-methyl-5- β -hydroxypropylthiazole are very much less active than the "natural" thiazole 4-methyl-5- β -hydroxyethylthiazole. Two thiamin analogues isothiamin and chlorothiamin (structures below) possessed about $\frac{1}{10,000}$ of the activity of thiamin for *Staph. aureus* (Knight and McIlwain, 1938). These results may be regarded as due to differences in the availability of the compounds for the synthesis of coenzymes or to the relative inactivity of the coenzymes which could be synthesised. The process may be carried one stage further; an analogue can be synthesised which is not simply inactive but instead is actively growth inhibitory, either because it prevents synthesis of the natural coenzymes, or because it is inadvertently utilised by the organism to synthesise a coenzyme analogue which is an enzyme inhibitor. These points will be considered more fully (p. 219) in discussion of competitive inhibition as an explanation of the bacteriostatic action of the thiamin analogue pyrithiamin (Woolley and White, 1943b).



ISO-thiamin



CHLORO-thiamin

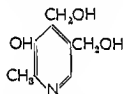
Riboflavin

Riboflavin is a component of a number of enzyme systems, particularly those concerned with cellular oxidation (Chapter II). As might be expected, it has been found to be an essential

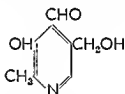
higher concentrations the compound acts as a growth inhibitor for *Lactobacillus casei*. The significance of the data given above can be more fully appreciated and their chemotherapeutic implications better elaborated, after a discussion of competitive inhibition in enzyme systems.

Pyridoxin, pyridoxal, pyridoxamine

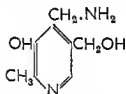
Pyridoxin (vitamin B₆) was first recognised as an essential metabolite in animal nutrition, and later found to be essential for various strains of bacteria, moulds, fungi and plants. Snell (1942) found that some bacteria responded less readily to pyridoxin than to a compound formed by autoclaving pyridoxin with cystine and glycine. Later, after the synthesis of pyridoxin and various related compounds, he found that for some strains of *Strep. lactis* the derivatives pyridoxal and pyridoxamine were 5000 to 8000 times as effective as pyridoxin



Pyridoxin



Pyridoxal



Pyridoxamine

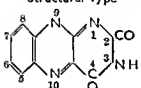
itself (Snell, 1944b). All three compounds exist in various types of cells (Snell, 1945a) and can probably be interconverted by most organisms. Why pyridoxal and pyridoxamine should be so much more active than pyridoxin for *Strep. lactis* has not been fully explained. With *Lactobacillus casei*, pyridoxal is about 1500 times as active as pyridoxin, and pyridoxamine only three to ten times as active. This difference, which can be used to distinguish between the three compounds (Snell and Rannefeld, 1945), may be due to differences in enzymic requirements of different cells, or it may be a permeability effect. Some micro-organisms, for example certain strains of lactic acid bacteria, grow well without added pyridoxin and have been shown to synthesise more than enough for their own requirements; others, such as *Leuconostoc mesenteroides* and *Staph. albus*, can grow slowly in absence of added pyridoxin but do not produce sufficient to allow maximal growth; for

grown on an amino acid glucose medium require thiamin or riboflavin but not both (Wood, Geiger and Werkman, 1940).

Various structural analogues of riboflavin have been tested for their ability to replace the vitamin in bacterial or animal nutrition. Some, as indicated in Table 9, can replace the natural product to a limited extent, others have

TABLE 9

Activity of riboflavin analogues as growth promoters and as coenzymes in isolated systems

Structural Type 	Growth Response		Coenzyme Function in Cell-free Enzyme Preparation
	<i>Lactobacillus casesi</i>	Rat	
6:7-dimethyl-9 (1'd-ribityl) .	++++	++++	++++
7-methyl-9 (1'd-ribityl) .	++	++++	++++
6-methyl-9 (1'd-ribityl) .	+	++++	+++
6-ethyl-7-methyl-9 (1'd-ribityl) .	+++	++++	—
6:7-dimethyl-9 (1'd-arabityl) .	± *	+	—
6:7-dimethyl-9 (1'l-arabityl) .	± *	+	++
6-ethyl-7-methyl-9 (1'l-arabityl) .	± *	+	...
6:7-dimethyl-9 (1'sorbityl) .	—	—	...
5:6-benzo-9 (1'd-ribityl) .	± *	—	..
5:6 dimethyl-9 (1'd-ribityl) .	± *	Inhibitor	...
6:7-dichloro-9 (1'd-ribityl) .	Inhibitor
6:7-dimethyl-9-galacto .	.	Inhibitor	..

* Positive response in presence of sub-optimal amounts of riboflavin.

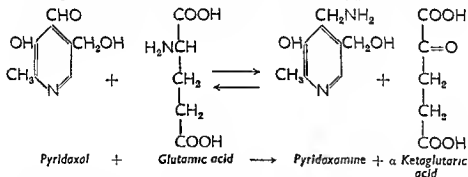
Data from:—Kuhn and Rudy (1936 *a* and *b*), Kuhn, Vetter and Rzeppa (1937); Kuhn, Weygand and Möller (1943); Snell and Strong (1939b); Möller (1940), Sarett (1946); Emerson, Wurtz and Johnson (1945); Emerson and Tishler (1944).

no activity, and others are actively growth-inhibitory. Activity can be related to some extent to coenzyme function, since Kuhn has tested a number of structural analogues on an isolated enzyme system (Kuhn and Rudy, 1936b; cf. Snell and Strong, 1939b; Möller, 1940).

If the sugar residue of riboflavin is removed altogether and replaced by a methyl group as in 6:7:9-trimethylisaloaxazine, most of the growth-promoting activity disappears and at

Convincing evidence has now been provided showing that pyridoxal phosphate is an essential coenzyme for four bacterial decarboxylases which act on tyrosine, lysine, arginine and ornithine (Gale and Epps, 1944; Baddiley and Gale, 1945; Gale, 1946; Umhreit, Bellamy and Gunsalus, 1945; Karrer and Viscontini, 1947 *a* and *b*; Gunsalus and Umbreit, 1947). The conditions necessary for production of the protein portion (apo-enzyme) of tyrosine decarboxylase have been investigated using pyridoxin-deficient media containing alanine (Bellamy and Gunsalus, 1945). The concentration in the medium of nicotinic acid, alanine, folic acid and purines, but not of thiamin, influenced the amount of apo-enzyme formed by the growing cells.

The decarboxylases are by no means universal cellular enzymes, and are probably much less important from the point of view of fundamental intermediary metabolism than the transaminases. The suggestion that pyridoxal is involved in transamination came from the observation of Snell (1945c), that on heating together glutamic acid and pyridoxal the following reaction took place. The same type of reaction

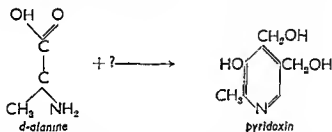


occurred with other amino acids and pyridoxal or with keto acids and pyridoxamine. Cell-free bacterial and animal extracts were found to catalyze transamination between certain amino and keto acids. The part played by pyridoxal in this reaction was confirmed by an examination of the effect of adding pyridoxal or pyridoxamine to pyridoxal-starved cultures of *Strep. faecalis*. The starved cells, grown in the presence of excess alanine, were almost devoid of transaminase activity, but addition of pyridoxal resulted in a rapid development of

these organisms pyridoxin acts as a growth stimulant (Bohonos, Hutchings and Peterson, 1942; Vilter and Spies, 1940).

As already indicated (Chapter II) pyridoxal has been found to be an essential component of enzymes concerned with amino acid decarboxylation and with transamination, and therefore with amino acid synthesis. These conclusions are amply confirmed by study of the metabolism of pyridoxin- or pyridoxal-starved cells and by the metabolic response induced by addition of these compounds.

Strep. faecalis will grow in the absence of pyridoxin if sufficient alanine is present in the medium (Snell and Guirard, 1943). The *l*-isomer of alanine (that occurring in protein) was only about one-sixth as active as the *d*-isomer which may function as a precursor of pyridoxin as shown in the accompanying scheme (Snell, 1945b; Shive and Shive, 1946).




Cells grown in the presence of excess alanine and sub-optimal amounts of pyridoxin provided useful material for the investigation of pyridoxin function and behaved as pyridoxin-starved cells. Their rate of glycolysis was normal and was not altered by addition of pyridoxin, but the rate of decarboxylation of tyrosine was very much below normal and was restored to normal by pyridoxal and, to a lesser extent, by pyridoxin. With *Strep. lactis* R., for which pyridoxin had low growth-promoting activity, addition of pyridoxin to starved cells had little effect on tyrosine decarboxylase activity, while pyridoxal was highly active. In cultures which had been dried, pyridoxal was no longer effective, but full restoration of decarboxylase activity followed addition of phosphorylated pyridoxal or pyridoxal plus adenosine triphosphate (Gunsalus and Bellamy, 1944 *a* and *b*; Gunsalus, Bellamy and Umbreit, 1944; Bellamy and Gunsalus, 1945).

requirements with respect to amino acids when pyridoxamine replaced pyridoxin in the medium (Stokes and Gunness, 1945). In *Neurospora*, pyridoxal phosphate acts as coenzyme in the synthesis of tryptophan from indole and serine; the enzyme catalysing the reaction has been prepared in a cell-free state (Umbreit, Wood and Gunsalus, 1946). In *Escherichia coli* the analogous reaction, transformation of tryptophan to indole plus pyruvic acid and ammonia, is catalysed by another

TABLE 10

Relation of structure of pyridoxin analogues to growth-promoting effect for Lactobacillus arabinosus

Structural Type			Relative Activities.
			
R ₁	R ₂	R ₃	
OH	CH ₂ OH	CH ₂ OH	1.0 (pyridoxin)
OH	CH ₂ OAc	CH ₂ OAc	0.8 to 1.0
OH	CH ₂ Br	CH ₂ Br	0.6 to 0.8
OH	CH ₂ OEt	CH ₂ OH	0.3
OH	CH ₂ OMe	CH ₂ OH	0.3 to 0.4
OH	CH ₃	CH ₂ OH	0.03
OH	CH ₃	CH ₃	0
OAc	CH ₂ OAc	CH ₂ OAc	0
NH ₂	CH ₂ OH	CH ₂ NH ₂	0
OH	CH ₂ OH	COOH	0

Data from Bohonos, Hutchings and Peterson (1942).

enzyme which also utilises pyridoxal phosphate as coenzyme (Wood, Gunsalus and Umbreit, 1947; see also p. 109). Pyridoxin also appears to be associated with synthesis or utilisation of thiamin (Stokes, Foster and Woodward, 1943).

Structural analogues of pyridoxin show varying degrees of activity as indicated in Table 10.

Pantothenic Acid

Pantothenic acid was first recognised as a growth factor for yeast and animals, and was identified, after isolation

a glutamate-aspartate transaminase system. The nature of the system was fully confirmed by demonstration of the conversion of added pyridoxamine into pyridoxal phosphate and by the activation of a cell-free enzyme preparation by either pyridoxamine phosphate or pyridoxal phosphate (Lichstein, Gunsalus and Umbreit, 1945; Umbreit, O'Kane and Gunsalus, 1946; Schlenk and Fischer, 1947).

The relative importance of the transaminase and decarboxylase functions of pyridoxal is indicated by the observation that cells growing at almost their normal rate in a suboptimal concentration of pyridoxin showed greatly reduced decarboxylase activity, but little or no reduction in transaminase activity. Transamination was not reduced until the pyridoxin content of the medium was considerably lower, when growth itself was also decreased (Lichstein, Gunsalus and Umbreit, 1945; Cohen and Lichstein, 1945). This provides an excellent example of the way in which a less essential enzyme (decarboxylase) can be dispensed with so that metabolites may be spared for their more essential functions.

There exists a close connection between pyridoxin requirements, carbon dioxide tension and amino acid requirements, which indicates that pyridoxin is involved in the synthesis of a number of amino acids through carbon dioxide fixation. At atmospheric carbon dioxide tension, *Strep. hemolyticus* will not grow in absence of pyridoxin, but at higher carbon dioxide tensions pyridoxin is unnecessary (Pappenheimer and Hottle, 1940). In the presence of excess carbon dioxide, pyridoxin can replace phenylalanine, tyrosine or arginine in the nutrition of *Lactobacillus arabinosus*, but at atmospheric carbon dioxide tension the omission of any one of these amino acids results in decreased growth which is not restored by additional pyridoxin (Lyman, Moseley, Wood, Butler and Hale, 1947). A similar effect has been found with aspartic acid in *Strep. faecalis*. Neither of these organisms possessed decarboxylases for the amino acids in question, so that growth must have been related to some reaction other than to decarboxylation. *L. arabinosus*, *L. casei*, and *L. delbrückii* all showed less exacting nutritional

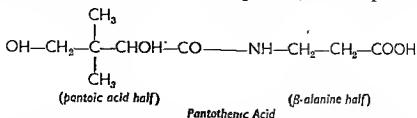
free acid by the cells; but addition of pantothenate to a cell-free yeast juice had no effect on the rate of glucose phosphorylation or fermentation (Teague and Williams, 1942).

Pantothenic acid is widely distributed and frequently occurs in cells in a "bound" or insoluble form. *Coenzyme A*, a coenzyme of general occurrence has been found to contain pantothenic acid, and probably accounts for a large part of the "bound" pantothenic acid of cells. *Coenzyme A* is essential for enzymic acetylation of aromatic amines and for the acetylation of choline in brain (Lipmann, Kaplan, Novelli, Tuttle and Guirard, 1947). Pantothenic acid supplied to *Lactobacillus arabinosus* or *Proteus morganii* is converted into coenzyme A and raises the rate of pyruvate oxidation in pantothenate-starved cells. In yeast also, added pantothenate is converted into coenzyme A and the uptake of pantothenate is accompanied by a greatly increased rate of acetate metabolism (Novelli and Lipmann, 1947 *a* and *b*). There is no doubt, therefore, that coenzyme A has a wide significance in metabolism, but the detail remains to be filled in.

Added pantothenate is inactivated by various organisms during both aerobic and anaerobic carbohydrate metabolism (McIlwain and Hughes, 1944, 1945). Inactivation is related to metabolism, but not to growth, in a way reminiscent of the usage of nicotinamide and the phosphopyridine nucleotides during metabolism. This has been ascribed by Lwoff and by Morel to a "wearing out" of successive molecules of coenzyme in consequence of the continuous oxidation and reduction of its molecule (Lwoff and Lwoff, 1937*b*; Morel, 1941). Pantothenic acid has been implicated also as necessary for the synthesis of tryptophan by *Staph. aureus* (Sevag and Green, 1944*a*).

Beside the essential metabolites to which definite enzymic or structural functions can be assigned, a number of other organic compounds have been found essential for animals and for growth of various nutritionally-exacting micro-organisms. The most important of these are biotin, *p*-aminobenzoic acid and folic acid. The functions of these substances have not yet

from liver, as $\alpha : \gamma$ -dihydroxy- $\beta : \beta$ -dimethylbutyryl- β -alanine (Williams, 1943). A few micro-organisms, for example *Lacto-*



bacillus casei and certain exacting strains of *Corynebacterium diphtheriae*, require the intact molecule and are unable to unite the two "halves" of the molecule if these are added to the medium (Evans, Handley and Happold, 1939; Evans, Happold and Handley, 1939; Happold, 1940). Other less exacting organisms, such as *Strep. haemolyticus*, can synthesise pantothenic acid if supplied with the component halves. Some strains of streptococci and *Clostridium septicum* have still greater synthetic powers and can synthesise the β -alanine half if supplied with the pantoic acid half (Woolley, 1939; Ryan, Ballentine, Stolovy, Corson and Schneider, 1945). Non-exacting strains of *Corynebacterium diphtheriae* may fail to synthesise β -alanine, but if supplied with this component can grow without pantothenic acid (Mueller and Cohen, 1937).

These results are closely reminiscent of the varied capacities existing among different micro-organisms for the synthesis of the two halves of the thiamin molecule. As with other essential metabolites, variation of structure may produce either a compound with lower growth-promoting activity, or one which is completely inactive, or even a compound which is growth-inhibitory (Snell, 1946; see also Chapter V).

Experiments on the effect of addition of pantothenic acid to "starved" organisms suggested that it might be concerned with pyruvate metabolism (Dorfman, Berkman and Koser, 1942; Hills, 1943). With deficient organisms using pyruvate as substrate, both oxygen uptake and anaerobic utilisation of pyruvate were greatly stimulated by added pantothenate; with glucose these effects were not apparent. Fermentation of pantothenate-deficient yeast cells was stimulated by added pantothenic acid and was accompanied by "binding" of the

free acid by the cells; but addition of pantothenate to a cell-free yeast juice had no effect on the rate of glucose phosphorylation or fermentation (Teagno and Williams, 1942).

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been correlated with any isolated enzyme systems, but it is probable that they will all be implicated as essential for various enzymic reactions.

Biotin

Biotin was originally recognised as a growth factor for yeast, but has subsequently been found to be essential for various clostridia, streptococci, staphylococci, pneumococci, lactobacilli and brucellæ. It is synthesised by other bacteria such as *Mycobacterium tuberculosis*, *Escherichia coli* and *Bacillus anthracis* (for full list see Knight, 1945; Peterson and Peterson, 1945).

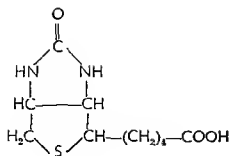
There is growing evidence for the metabolic function of biotin. du Vigneaud has suggested that it is involved in synthesis of some nitrogenous cellular material (Winzler, Burk and du Vigneaud, 1944). Biotin-deficient yeast cells were found to respire and ferment glucose at rates from one-tenth to one-twentieth of normal biotin-rich cells. The addition of biotin alone to the deficient cells had no effect, but biotin and ammonia caused a gradual rise in fermentation rate, followed by an increase in respiratory rate, and finally by an increase in growth rate. Biotin and ammonia were removed from the medium by deficient cells, but only if glucose was present, ammonia was not essential to biotin uptake. Azide, which is known to inhibit biosynthesis, prevented ammonia uptake at low concentrations.

Many lactic acid bacteria require both biotin and aspartic acid for growth and can be induced to grow without aspartic acid by increasing the biotin content of the medium (Stokes, Larsen and Gunness, 1947). Aspartic acid is not able to replace biotin for these organisms, so that biotin has probably some function other than promoting aspartic acid synthesis. The mechanism of the biotin-sparing action of aspartic acid is suggested by a report that oxaloacetic acid, a precursor of aspartic acid, also promoted growth of biotin-deficient lactobacilli. Synthesis of oxaloacetate by a number of heterotrophic organisms involves carbon dioxide fixation (see p. 77). Lardy, Potter and Elvehjem (1947) found that,

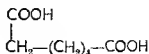
in a biotin-deficient medium, additional bicarbonate elicited no response, but that, in the presence of biotin, additional bicarbonate stimulated growth. The fixation of carbon dioxide in the form of oxaloacetate by carboxylation of pyruvate also seems to require biotin in yeast cells. In *Escherichia coli*, α -ketoglutaric acid or glutamic acid had a biotin-sparing effect when biotin synthesis was inhibited by imidazolidonecaproic acid (Fig. 15) (Shive and Rogers, 1947).

Degradation products and structural analogues of biotin promote growth in some micro-organisms and may have growth-inhibitory effects on others. The compounds to be discussed are depicted and numbered in Fig. 15.

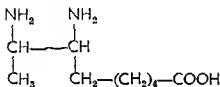
Pimelic acid (II) is a growth factor for some strains of *Corynebacterium diphtheriae*, but can be replaced by lower concentrations of biotin. Such strains only lack the ability to synthesise the fatty acid, and if supplied with this can convert it to biotin. Desthiobiotin (V) had full biotin activity for some yeasts, but with the more exacting *Lactobacillus casei*, *Lactobacillus arabinosus* or *Staph. aureus* it not only failed to support growth but even acted as a growth inhibitor (Dittmer, Melville and du Vigneaud, 1944; Lilly and Leonian, 1944). *Neurospora* and exacting X-ray "mutants" of *Escherichia coli* or *Penicillium notatum* were able to use desthiobiotin in place of biotin; but a mutant of *Penicillium chrysogenum* was unable to utilise desthiobiotin, and synthesis and accumulation of desthiobiotin by this organism was demonstrated (Tatum, 1945b). Biotin diamino acid (IV) had some growth-promoting activity for yeast, and this was dependent on the carbon dioxide partial pressure, as might be expected if carbon dioxide acts as a source of carbon to complete the ring (Burk and Winzler, 1943). Diaminopelargonic acid (III) had about 10 per cent. of the activity of biotin for yeast, but was inactive for other organisms. Imidazolidonecaproic acid (VII) was growth-inhibitory to *L. casei* and to yeast, whereas the lower homologue, imidazolidonevaleric acid, was a poor growth factor for yeast and had no effect on *L. casei*. Biotin sulphone (VI) also possessed feeble growth-promoting activity for yeast, but was growth-inhibitory for *L. casei*



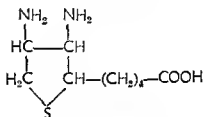
I. Biotin



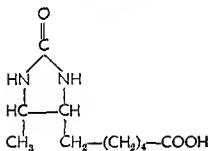
II. Pimelic acid



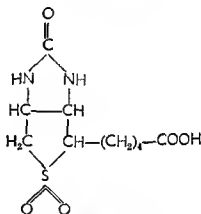
III. Diaminopimelic acid



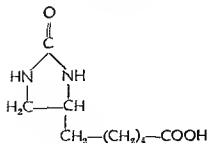
IV. Biotin diamine acid



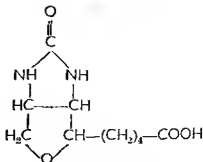
V. Desthiobiotin



VI Biotin sulphone



VII. Imidazolidonecaproic acid



VIII. Oxybiotin

FIG. 15.—Biotin Analogues.

(Dittmer and du Vigneaud, 1944). Oxybiotin (VIII), the analogue in which the sulphur atom is replaced by oxygen, showed up to 50 per cent. of the growth-promoting activity of biotin for both yeast and *L. casei* (Pilgrim, Axelrod, Winnick and Hofmann, 1945; Rubin, Flower, Rosen and Dreker, 1945). Evidently oxybiotin can be utilised by yeast without preliminary conversion to biotin, since yeast grown on oxybiotin was found to contain oxybiotin in place of biotin (Hofmann and Winnick, 1945; Axelrod, Flinn and Hofmann, 1947).

These results demonstrate effectively the narrow distinction between essential metabolites and metabolite analogues; the latter may be classed as growth factors, growth-factor precursors, or growth inhibitors according to the metabolic capacities of the organisms studied. We shall return to these and related examples when discussing the design of chemotherapeutically-effective metabolite analogues in Chapter V.

p-Aminobenzoic acid and folic acid

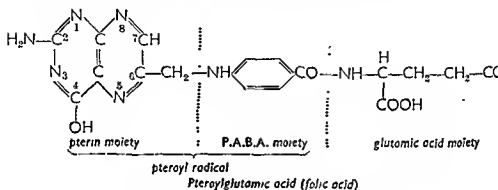
p-Aminobenzoic acid (P.A.B.A.) was found to be a growth factor only after Woods (1940) had shown that it acted as a powerful and specific antagonist to sulphanilamide (Chapter V). On the basis of this finding Woods suggested that P.A.B.A. was an essential metabolite.

The majority of micro-organisms are able to dispense with P.A.B.A. in their growth media; some of these have been found to synthesise their own supply (Landy, Larkum and Oswald, 1943). A few bacteria, including some strains of *Corynebacterium diphtheriae*, *Clostridium acetobutylicum*, *Lactobacillus arabinosus* and *Acetobacter suboxydans*, have been found to require an external supply of P.A.B.A. (cf. Knight, 1945; Sarett, 1947).

One function of P.A.B.A. has been elucidated following the disclosure of the structure (see formula) of folic acid (pteroyl-glutamic acid) (Angier *et al.*, 1946; Mowat *et al.*, 1948). Various bacteria synthesise folic acid, and P.A.B.A. is required for this synthesis (Sarett, 1947).

Discovery of the wide distribution of folic acid and

recognition of its biological importance represented the confluence of many diverse researches on bacterial growth factors and on animal nutrition (review by Piffner and Hogan, 1946). Various forms of pteroylglutamic acid have been identified in which more than one molecule of glutamic acid is present; pteroyltriglutamate and pteroylheptaglutamate have been isolated from yeast (Piffner, Calkins, Bloom and O'Dell,



1946). These forms have been identified with one or other of the nutritional factors—vitamin B_{12} , vitamin B_{12} conjugate, yeast *L. casei* factor, liver *L. casei* factor, etc. The different-sized peptides show varying relative activities with micro-organisms, probably because some cells can degrade the larger peptides easily, whereas others are unable to do so. A carboxy-peptidase type of enzyme which can degrade pteroylheptaglutamate to pteroylmonoglutamate has been identified in animals and in yeast (cf. Hutchings *et al.*, 1948).

Some micro-organisms require folic acid and are unable to synthesise it for themselves (Daniel, Norris, Scott and Heuser, 1947), others synthesise their own requirements. P.A.B.A. is an essential growth factor for *L. arabinosus*. Growth of *L. arabinosus* in the presence of P.A.B.A. is accompanied by the synthesis of pteroylglutamic acid, but pteroylglutamic acid can replace P.A.B.A. only to a very limited extent (Sarett, 1947). This suggests that P.A.B.A. has other functions in the organism besides the synthesis of pteroylglutamic acid.

With an essential metabolite of the molecular complexity of folic acid, the full detail of its structural specificity will

take some time to work out, but it is already apparent that some pteroylglutamic acid analogues possess limited growth-promoting properties and that others are growth inhibitory. N-(4-(4-quinazoline)-aminobenzoyl)-glutamic acid has from one-tenth to one-hundredth of the activity of folic acid for *Lactobacillus casei* (Martin, Moss and Avakian, 1947). Several 2:4-diaminopterins (for numbering see formula) inhibit growth of *Strep. faecalis* and *L. casei* which require preformed folic acid, and also *L. arabinosus*, *Escherichia coli* and *Staph. aureus* which synthesise their own supply (Daniel, Norris, Scott and Heuser, 1947; Daniel and Norris, 1947). A full discussion of the relationship between P.A.B.A., folic acid, sulphonamides and other inhibitors of folic acid synthesis is deferred until Chapter V. There is considerable evidence of a relationship between folic acid, purine and pyrimidine synthesis, but more information will have to be collected before the position becomes clear (see pp. 203-213). One hint of a possible coenzyme function for folic acid is provided by the report that 7-methylfolic acid acts as an inhibitor of "dopa" decarboxylase and that inhibition is reversed by folic acid (Martin and Beller, 1947).

Conclusion

Substances probably act as growth inhibitors because they are in one way or another enzyme inhibitors. The classification of a compound as an essential metabolite, is equivalent to saying that it is a constituent part of some enzymic system within the cell, and that enzymes must exist which are specifically designed to "fit" the particular chemical arrangement characteristic of the metabolite. If the enzyme is presented with a compound of closely related structure which can "fit" it the same way, but which is nevertheless in some other respect unusable for the functions normally performed by the metabolite, then the metabolite analogue may act as a growth inhibitor. The most important groups of metabolite analogues from the chemotherapeutic point of view are discussed more conveniently after a general review of the

characteristics of enzyme inhibition and of the possible ways in which various types of enzyme inhibition may differ.

It should be kept in mind that not only coenzyme or prosthetic group analogues may function in this way. Any molecule whether organic or inorganic, may resemble a functional metabolite in such a way that it is caught up in the overall catabolism and anabolism of the living cell, and may form in some metabolic chain a non-functional break which will upset the finely balanced processes of life and lead to death or to failure of reproduction.

We have on several occasions drawn attention to the capacity of an organism to dispense with what are apparently essential growth factors when placed in different media. This capacity should be kept in mind when considering the mode of action of chemotherapeutic drugs. Pathogenic organisms in their natural state, as parasites on the tissues of a host, can draw upon a multitude of nutrients, and the growth-inhibitory action of a drug may be overcome by a shift in metabolic balance which eliminates the strain's need for the drug-sensitive enzyme system. Such an altered balance may not be possible in a limited synthetic medium so that a drug effective *in vitro* may be useless *in vivo*, or rapidly rendered useless by the development of drug resistance.

CHAPTER IV

ENZYME INHIBITION

WE have attempted to build up a composite, but admittedly incomplete, picture of intermediary metabolism of living cells, particularly of bacterial cells as shown by their nutritive requirements. Examination of this picture may help in elucidating the mode of action of known chemotherapeutic drugs and in developing new ones. First, it is essential to deal briefly with the kinetics of enzymic reactions and also to study more fully the subject of enzyme inhibition, so that we can distinguish between the various types of inhibition known to occur.

Enzyme kinetics

The velocity of enzyme-catalysed reactions follows certain general rules which may be applied to most enzymes. At controlled pH and temperature, the velocity is constant during the early part of the reaction, but subsequently declines progressively with time due to exhaustion of substrate, accumulation of end-products and other causes. Unless otherwise stated, the velocity of enzymic reactions is always measured during this initial period when it is constant.

Each enzyme has a certain optimal pH at which it reacts most rapidly with a particular substrate. There is also usually an optimal temperature for each enzyme, above which heat-inactivation of the enzyme plays a part in determining the reaction velocity. With low substrate concentrations, velocity is proportional to both enzyme and substrate concentration, but with increasing substrate concentration a maximal velocity is reached which is no longer dependent on substrate concentration, being proportional only to enzyme concentration (Fig. 16). Enzymic reactions are reversible; the effect of enzymes, like all catalysts, is to speed the attainment of equilibrium but not to alter the position of equilibrium.

Theoretically, enzymic reactions should conform to the law of mass action, with velocity proportional only to substrate concentration. We have already seen that this is not the case, and Fig. 16 shows a comparison between the velocities of two reactions, one enzymic and one following the law of mass action. This discrepancy was first explained satis-

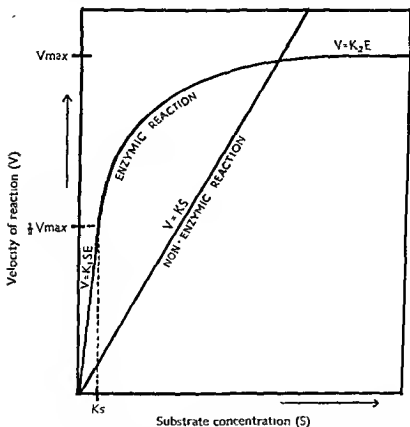
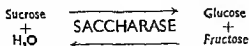


FIG 16.—Effect of substrate concentration on reaction velocity; enzymic and non-enzymic reactions.

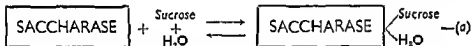
factorily by Michaelis and Menten (1913), who assumed that enzyme and substrate combine reversibly to form an intermediate complex. Applying the law of mass action to this reversible reaction, they obtained an equation, known as the Michaelis-Menten equation, for variation of speed of reaction with substrate and enzyme concentrations. This equation provides both adequate explanation of much experimental

data, and useful constants for the characterisation of individual enzymes.

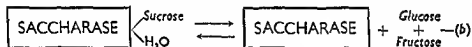
The derivation of the Michaelis-Menten equation can be explained by reference to the enzyme saccharase as an example; this catalyses the following overall reaction:—



According to the Michaelis theory, the reaction proceeds in two stages: (a) one molecule of sucrose and one of water combine with one molecule of enzyme to form a complex in equilibrium, according to the law of mass action, with its constituents;



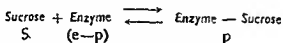
(b) the intermediate complex splits to form the reaction products glucose and fructose, and unchanged enzyme. The assumption



is made that the rate of reaction, at any time, is governed by the concentration of the onzy-mo-substrate complex, since the rate of formation of this complex (reaction a) is very much more rapid than that of its decomposition into reaction products (reaction b). Thus the concentration of complex may be obtained by applying the law of mass action to reaction (a) alone.

The reaction proceeds in aqueous solution, thus the concentration of water is infinito in comparison to that of the other reactants and can be neglected.

Reaction (a) may therefore be represented as



Let S = concentration of sueroso

e = concentration of total enzyme

p = concentration of enzyme-sucrose complex

$e-p$ = concentration of free enzyme.

K_s (the dissociation constant of the enzyme-substrate complex) is known as the *Michaelis constant*; it represents an important constant which is independent of enzyme and substrate concentration and is characteristic of each enzyme. K_s may be considered to represent a measure of the affinity of an enzyme for its substrate. When $V = \frac{1}{2}V_{\max}$, $K_s = S$; that is, K_s is numerically equal to substrate concentration when the velocity is half the maximum value (see Fig. 16).

An accurate knowledge of K_s and V_{\max} are essential in characterising an enzyme. They could, of course, be obtained from equation (5) by plotting velocity against substrate concentration as in Fig. 16. A less laborious and more accurate method suggested by Lineweaver and Burko (1934) is to plot the reciprocals of velocity and substrate concentration and so obtain a straight line whose equation (6) is derived from equation (4).

$$\frac{1}{V} = \frac{K_s + S}{V_{\max} S}$$

$$\text{i.e.} \quad \frac{1}{V} = \frac{K_s}{V_{\max}} \cdot \frac{1}{S} + \frac{1}{V_{\max}} \quad (6)$$

The slope of this line is $\frac{K_s}{V_{\max}}$, while its intercept on the $\frac{1}{V}$ axis is equal to $\frac{1}{V_{\max}}$ (see Fig. 17).

The above theory and the formulæ derived from its application have proved adequate to cover the kinetic data for many enzymic reactions; Stearn (1938) concludes that the Michaelis constant may possess real thermodynamic significance. However, as might be expected from the enormous variety of enzymic reactions, not every case will fit into the mould prepared by Michaelis and Menten. Various explanations have been put forward to explain these anomalies (Wilson, 1939). Briggs and Haldane (1925) pointed out that the assumption is not always justified that formation of the intermediate enzyme-substrate complex is infinitely rapid compared to its rate of decomposition into enzyme and reaction products; in certain cases rate of formation of the complex might be limited by the number of collisions in the

bi-molecular reaction $\text{Enzyme} + \text{Substrate} \rightarrow \text{Complex}$. The application of chain reaction theory has led to an expression derived by Moelwyn-Hughes (1933, 1937, 1940) for velocity of reaction; Medwedew (1937) replaced the intermediate

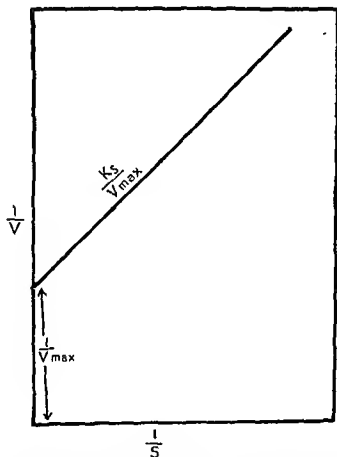


FIG. 17.—Variation of reciprocal of velocity ($1/V$) of enzymic reaction with reciprocal of substrate concentration ($1/S$) (Enables V_{\max} , maximum velocity, and K_s , dissociation constant of enzyme-substrate complex, to be calculated graphically.)

complex theory by one based on quantum mechanics in which there is no formation of a definite complex between enzyme and substrate; Stearn (1938) applied quantum mechanics to enzyme-substrate complex. Each of these theories explains some anomaly in the kinetics of certain enzyme reactions, but they all (including that of Michaelis and Menten) predict

equally satisfactorily the same set of experimental data (e.g. Fig. 16) derived from the more common enzymic reactions. Therefore one must conclude that, in this field, agreement between experimental and predicted data does not constitute proof of a theory. For most practical purposes, the Michaelis-Menten theory and equations may be used to derive characteristic enzyme constants, and as we shall see later, also provide explanations of the phenomena of enzyme inhibition.

Enzyme-substrate complex

The question of the reality of existence of an enzyme-substrate complex is of importance in connection with the phenomena of enzyme inhibition as well as in the derivation

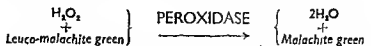
645	PEROXIDASE	583	548	498
H ₂ O ₂ PEROXIDASE		561	530.5	

FIG. 18.—Positions of absorption bands of peroxidase and H₂O₂-peroxidase compound. (Keilin and Mann, 1937)

of the velocity constants of enzymic reactions. Direct evidence has been difficult to obtain because of the extremely short life of the complex, but work with peroxidase has shown that, in the case of this enzyme at any rate, a definite complex is formed (Keilin and Mann, 1937). Peroxidase is a hæmatin-containing enzyme which decomposes hydrogen peroxide in the presence of an oxidisable compound to which it transfers one atom of oxygen. Its spectrum conforms to that of an iron-porphyrin compound in the ferric state with absorption bands at 645 m μ , 583 m μ , 548 m μ , and 498 m μ . On addition of hydrogen peroxide to a strong solution of peroxidase, the original brown colour of the solution is changed to a clear red and the four-banded absorption spectrum is replaced by two bands at 561 and 530.5 m μ (Fig. 18). The amount of peroxide necessary to effect such a change corresponds to one molecule per atom of porphyrin iron. In the absence of an oxygen

acceptor the two-banded form of peroxidase is fairly stable, but on addition of pyrogallol the four-banded spectrum immediately reappears. The evidence suggests that enzyme and substrate are here combining to form a compound whose spectrum differs from that of the free enzyme.

This work has been extended by Chance (1943) using leuco-malachite green as an oxygen acceptor. A photo-electric



recording device measuring rapid changes in absorption at suitable wave lengths enabled the velocity of formation and dissociation of the peroxidase- H_2O_2 complex to be determined. These velocities were found to follow bi-molecular reaction laws; complex formation was extremely rapid, while the reverse reaction was relatively slow. The rate-determining step of the overall reaction was a much slower monomolecular decomposition of the complex into enzyme and reaction products. These experiments provide proof of the two main assumptions on which Michaelis based his theory, namely formation of enzyme-substrate complex, and the dependence of rate of reaction on speed of decomposition, not of formation, of this complex. It would appear then that for our purpose, the Michaelis treatment of enzyme kinetics is adequate.

The prosthetic groups of some enzymes are sufficiently firmly bound to the protein portion of the molecule to be regarded as part of the complete enzyme as in the case of peroxidase. In other enzymes, such as the pyridine nucleotide dehydrogenases, the prosthetic group is easily dissociated and is usually referred to as a coenzyme. In such cases, the coenzyme can be regarded as a second substrate undergoing reversible combination with the protein molecule, and its reactions are therefore subject to the same kinetic treatment as the enzyme-substrate complex itself.

Non-specific enzyme inhibition ; "SI inhibition"

Enzymes are generally assumed to combine with their substrates by means of their "active centres" or "active

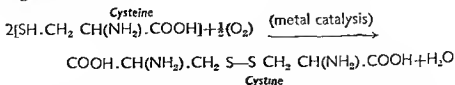
groups." Little is known about the nature of these active centres, but it is likely that they are responsible for the highly specific effect of each enzyme. For the purpose of visualising the combination of enzyme with its substrate, the lock and key theory propounded by Fischer (1894) is still of value, since it emphasises that the configuration of both enzyme and substrate must conform to a certain pattern. This is well illustrated by the work of Bergmann and his school on proteolytic enzymes and the optical configuration of their substrates. Certain of these enzymes, such as carboxypeptidase, are incapable of hydrolysing synthetic peptides whose terminal amino acids are of the *d*-configuration, although the *l*-antipodes are extremely sensitive to action of the enzyme (Stahmann, Fruton and Bergmann, 1946).

It is reasonable to conclude that any substance which reacts with an essential group at the active centre of the enzyme, will inhibit by rendering the enzyme incapable of combining with or activating its substrate. As we shall see, this inhibitory effect is not confined to substances reacting only with the active centre, and it is probable that certain other groupings in the enzyme are also essential for maintenance of activity. Langenbeck (1935), from a study of the catalytic properties of certain synthetic organic compounds, suggested that a distinction should be drawn between the active centre at which substrates react and the surrounding groups in the molecule which may have an activating effect on the active centre. Such a concept is also useful in the case of enzymic catalysis, and should be borne in mind in the ensuing description of enzyme inhibition.

Any substance which causes irreversible denaturation of proteins in general will act as a non-specific enzyme poison, and is of no interest either for theoretical consideration of enzyme inhibition or as a chemotherapeutic drug. On the other hand, selective reagents which react with free carboxyl, hydroxyl, amino and sulphydryl groups of proteins should yield valuable information as to the nature of essential groups, provided pure enzymes are employed. Careful choice of reagent may result in blocking or alteration of one or more of certain

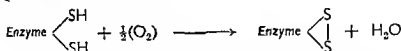
reactive groups of an enzyme without affecting other groups. For example, the use of nitrous acid and ketene, which react with amino and aromatic hydroxy groups, has shown that free amino groups are not essential for activity of β -amylase, pepsin or chymotrypsin, but that free tyrosine hydroxy groups are essential (Weill and Caldwell, 1945; Philpot and Small, 1938; Herriott and Northrop, 1934; Herriott, 1935, 1936; Sizer, 1945). Free amino groups have, however, been found necessary for activity of pancreatic amylase and alkaline phosphatase (Little and Caldwell, 1943; Gould, 1944). Iodine has also been used to demonstrate the essential nature of free tyrosine hydroxyl radicals in pepsin; Li (1945) found that out of the total 17 tyrosine residues present in the molecule, only 12 were free to react with iodine.

Selective attack or blocking has yielded the most fruitful results in the case of sulphhydryl groups, which have been thus found essential for activity of many enzymes. Sulphydryl groups are highly reactive, combining with a variety of reagents, and are also susceptible to oxidation by mild oxidising agents. This reactivity is illustrated by the case of the amino acid cysteine, which is a main source of sulphhydryl groups in proteins. In air, solutions of cysteine are rapidly oxidised in the presence of catalytic amounts of metals, but are stable in the complete absence of metals. The product of oxidation is cystine, the corresponding disulphide derivative; reducing agents reverse the reaction, and free sulphhydryl groups are regenerated.

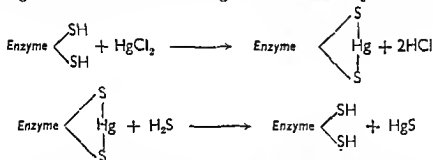


Many enzymes have been known for some time to be susceptible to the action of mild oxidising and reducing agents (see review by Hellerman, 1937), but the earlier reports related only to crude enzyme preparations and led to no acceptable theory for the mechanism of this effect. However, in 1933, Hellerman observed that highly purified crystalline

urease was extremely easily inactivated in air by catalytic traces of heavy metals in the solution; iodine-iodide mixtures had a similar effect. Both inactivations could be reversed by reducing agents. Working by analogy with cysteine, he suggested that these inactivations of urease were due to oxidation of sulphydryl groups essential for enzyme activity (Hellerman, Perkins and Clark, 1933). The change may be represented as follows:—



This suggestion explained earlier observations of numerous investigators on the inactivation of urease by salts or ions of heavy metals, since the reactive sulphydryl groups could combine readily with metallic ions to form mercaptide linkages. This inactivation might be reversed by an excess

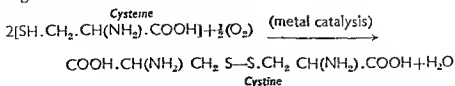


of some substance capable of forming a less dissociable or an insoluble compound with the metal. Such conditions occur in the long-known reactivation of urease by cyanide or hydrogen sulphide. The activating effect of reducing agents on the plant proteolytic enzyme papain was also explained in 1933 by Bersin as a reduction of —S—S—linkages to the sulphydryl form. In confirmation of this, he found that papain was inhibited by trivalent organic arsenical compounds, the inhibition being reversed by glutathione (Bersin, 1933; Bersin and Logemann, 1933).

Since this preliminary work, the activity of numerous enzymes has been shown by many investigators to be dependent on free sulphydryl groups, and the term "*SH enzymes*" is now widely applied to any such enzyme (see Barron, 1943, and

reactive groups of an enzyme without affecting other groups. For example, the use of nitrous acid and ketene, which react with amino and aromatic hydroxy groups, has shown that free amino groups are not essential for activity of β -amylase, pepsin or chymotrypsin, but that free tyrosine hydroxy groups are essential (Weill and Caldwell, 1945; Philpot and Small, 1938; Herriott and Northrop, 1934; Herriott, 1935, 1936; Sizer, 1945). Free amino groups have, however, been found necessary for activity of pancreatic amylase and alkaline phosphatase (Little and Caldwell, 1943; Gould, 1944). Iodine has also been used to demonstrate the essential nature of free tyrosine hydroxyl radicals in pepsin; Li (1945) found that out of the total 17 tyrosine residues present in the molecule, only 12 were free to react with iodine.

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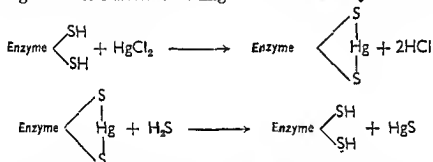


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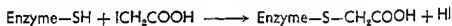
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Barron and Singer, 1945 *a* and *b*, for list of such enzymes). Many reagents are employed to detect essential sulphydryl groups, among which, the most active and specific are the organic mercaptide-forming reagents such as *p*-chloromercuribenzoate (introduced by Hellerman) and the trivalent arsenoxides. Mild oxidising agents like porphyrindin, ferricyanide and *o*-iodosobenzoate, when acting under carefully controlled conditions, may also be used to attack sulphydryl groups specifically. The inactivation caused by both mercaptide-forming reagents and oxidising agents is reversed by low molecular weight thiols such as cysteine or glutathione; this reversal should always be included as a further diagnostic test for "SH enzymes." Alkylating agents such as iodoacetate, iodoacetamide and bromoacetate were frequently used by earlier investigators in tests for "SH enzymes." Iodoacetate was shown by Dickens (1933) to react stoichiometrically with sulphydryl-containing compounds such as glutathione, and it is now generally believed to react with sulphydryl groups of proteins by alkylation. This reaction is, however, irreversible and not entirely specific to sulphydryl groups.



Not all enzymes now known to require sulphydryl groups for activity are equally easily inactivated by iodoacetate or oxidising agents. Thus, iodoacetate at low concentrations ($M/3000$) is known to be an extremely potent inhibitor of yeast fermentation by reason of a specific inhibition of alcohol dehydrogenase (Dixon, 1937). Many other enzymes concerned in alcoholic fermentation are "SH enzymes" (see Barron, 1943), but none are inhibited by this concentration of iodoacetate. This must be due to differences in reactivity of sulphydryl groups caused by the configurations of the different enzymic proteins. This variation in reactivity is illustrated in the case of papain and urease. Papain is inactivated by iodoacetate, yet only one out of the total of 10 sulphydryl groups is alkylated by this reagent (Balls and Lineweaver, 1939). On the other hand, when crystalline urease was treated with one mole of *p*-chloromercuribenzoate per 21,300 g.

of enzyme no loss in activity occurred, but a second mole of reagent produced loss in activity, although only 2 out of a total of 5 sulphydryl groups were then combined; the remaining 3 sulphydryl groups could only be attacked after denaturation of the protein (Hellerman, Chinard and Deitz, 1943). Urease is not inactivated by porphyrindin, yet once oxidised by this reagent, it only requires one mole of *p*-chloromercuribenzoate for inactivation. These experiments suggest that urease contains 3 types of sulphydryl groups: a freely reactive one which is not essential for activity, another which is less reactive but essential for activity, while the third type is not free to react in the native protein and is only uncovered during the unfolding of the protein chains, which accompanies denaturation. Great differences occur in the susceptibility of various SH-enzymes to arsenical compounds. The war gas lewisite, $\text{Cl}\cdot\text{CH}=\text{CH}\cdot\text{AsCl}_2$, was found to be highly toxic for most SH-enzymes tested; organic trivalent arsenical drugs were less toxic, and arsenites were least effective. Three SH-enzymes were, however, almost unaffected by lewisite (Barron *et al.*, 1947).

The actual role played by sulphydryl groups in enzymes is still unknown; in several cases, however, there is evidence that they do occur at the active centre of the enzyme. Thus, succinic dehydrogenase is not inhibited by "SH inhibitors" if succinic or malonic acid is already present (Hopkins, Morgan and Lutwak-Mann, 1938; Potter and DuBois, 1943; Barron and Singer, 1945a). Phosphoglyceraldehyde dehydrogenase is protected to some extent by its coenzyme (diphosphopyridine nucleotide) from inhibition by "SH inhibitors" (Rapkine, 1938), while the inhibition of *D*-amino acid oxidase by *p*-chloromercuribenzoate is partly prevented by the presence of excess of its coenzyme (flavin adenine dinucleotide) (Hellerman, Lindsay and Bovarnick, 1946). In these cases, combination of the enzyme with either coenzyme, substrate, or substrate-analogue evidently reduced access of inhibitor to sulphydryl groups, and it is probable that here sulphydryl groups are playing an essential part in the formation of enzyme-substrate complex.

Whatever the role played by sulphydryl groups, it is evidently an important one for maintenance of enzymes in an active state. Glutathione can effect complete reversal of inactivation by *p*-chloromercuribenzoate only if it is added within ten to fifteen minutes after addition of the mercurial to the enzyme. After this time, reversal is not complete, the degree of reversal being decreased with increasing time interval between addition of inhibitor and antidote (Barron and Singer, 1945a).

With the realisation of the importance and widespread nature of enzymes depending for activity on sulphydryl groups, it is reasonable to assume that any substance capable of reacting with such groups may be a potential enzyme inhibitor. Conversely, any substance with chemotherapeutic activity possessing the capacity to link with reactive hydrogen may act by addition to certain sulphydryl groups of enzymes. Metal oxides or metal ions, quinones, ketones, acids or nitriles with $\alpha : \beta$ -unsaturation might be expected to act in this way. Their selective action, whereby some "SH enzymes" are inhibited by certain reagents and others are not, is probably due to differences in accessibility of the essential sulphydryl groups of various enzymes.

Specific inhibition ; competitive and non-competitive

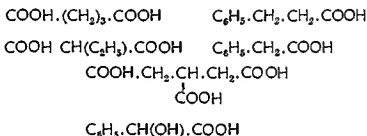
So far we have dealt with types of inhibition which are relatively non-specific in that they are concerned with certain groupings common to many enzyme proteins. If an inhibiting agent proves to be specific to one enzyme or group of enzymes, it may reasonably be assumed to interfere with a reaction or grouping specific to those enzymes. Enzymic specificity is related to the active centre, which is so constituted as to combine selectively with the substrate. Therefore, any substance which prevents either this combination or the activation of substrate on the enzyme surface may act as a specific inhibitor to the enzyme in question. We may envisage several ways by which such inhibition could be brought about. Access of either coenzyme or substrate to the active centre may be prevented by alteration or blocking of the centre

itself, or the coenzyme or the prosthetic group may be modified so that it is incapable of performing its function.

Alteration of prosthetic group is responsible for inhibition of the haematin enzymes, such as cytochrome oxidase and catalase, by carbon monoxide, hydrogen sulphide, cyanide, azide or hydroxylamine. The inhibition of glycolysis by fluoride is now known to be due to reaction with magnesium, a coenzyme of enolase (Warburg and Christian, 1942). Fluoride had long been known to be a powerful specific inhibitor of glycolysis, causing accumulation of phosphoglyceric acid (Emden and Ickes, 1934). When Warburg crystallised the enzyme enolase which acts on phosphoglyceric acid, he found, as expected, that it was strongly and specifically inhibited by fluoride. The mechanism of inhibition was shown to be through formation of a magnesium-fluoro-phosphate complex which inhibits the action of the enzyme by itself combining with enzyme protein. The inhibition of certain metalloprotein enzymes by 2:3-dimercaptopropanol (B.A.L.) and other dithiols is also due to combination of metal with inhibitor (Webb and van Heyningen, 1947; Barron, Miller and Meyer, 1947).

In many cases the specificity of an enzyme for its substrate or coenzyme is not absolute, and the enzyme is capable of combining through its active group with other substances structurally related to either substrate or coenzyme. However, it is unable to activate these substances and is consequently inhibited because access to the active group is prevented. In other words, a competition for the active group exists between inhibitor and substrate or coenzyme. The term *competitive inhibition* is therefore applied to the phenomenon, which is of considerable importance in enzyme chemistry. Malonic acid, the lower homologue of succinic acid, inhibits succinic dehydrogenase by preventing access of succinic acid to the enzyme. This can be shown by increasing the ratio of succinic acid to malonic acid in the reaction system; the degree of inhibition is then decreased, owing to displacement by succinic acid of some of the malonic acid in combination with the enzyme. With sufficient succinic acid, the inhibition can be completely overcome (Hopkins, Morgan

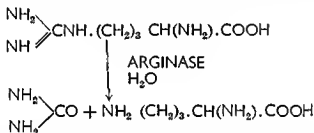
and Lutwak-Mann, 1938). Combination of inhibitor with enzyme is easily reversible, and the degree of inhibition for a given amount of enzyme is related to the concentration of substrate as well as to the inhibitor concentration. These are characteristic properties of true competitive inhibition and are used to identify the phenomenon both *in vitro* and *in vivo*. Malonic acid acts as a very specific inhibitor *in vivo* of succinic dehydrogenase; its use in this respect has already been referred to in considering the tricarboxylic acid cycle (p. 80). Some other substances related to succinic acid which have been found to inhibit succinic dehydrogenase are



(Quastel and Wooldridge, 1928). Many other cases of competitive inhibition are known, among which may be cited the inhibition of diamine oxidase by certain long-chain diamines (Blaschko and Duthie, 1945b); the inhibition by glucose of the phosphorylase synthesising glycogen from glucose-6-phosphate (Cori, Cori and Green, 1943); and the inhibition by pyridine sulphonic acid of glucose and lactic acid dehydrogenases both of which work through coenzyme I (Euler, 1942). In the latter case, the coenzyme is displaced from combination with enzyme protein by the sulphonic acid analogue of the coenzyme; in the two former cases, it is the substrate which is in competition with inhibitor.

Another type of specific and reversible inhibition is frequently encountered, in which degree of inhibition is not related to substrate concentration, but only to inhibitor concentration. This suggests that the substrate cannot prevent combination of inhibitor with enzyme. Therefore, the inhibitor must combine with some grouping which does not itself combine with the substrate but which is essential for

substrate-activation. This type of inhibition is usually referred to as *non-competitive*, to distinguish it from competitive inhibition. Like competitive inhibition, it is also displayed by substrate analogues, but when both competitive and non-competitive inhibition of an enzyme occur with different inhibitors, those analogues giving rise to competitive inhibition usually resemble the substrate more closely than those causing non-competitive inhibition. Such is the case in the inhibition of arginase by amino acids, studied by Hunter and Downs (1945). This enzyme catalyses the splitting of arginine to urea and ornithine. The diamino acid lysine inhibits the action



of arginase in a competitive manner, the degree of inhibition for a given enzyme concentration being dependent on inhibitor/arginine ratio. Monoamino acids, on the other hand, show non-competitive inhibition, where substrate concentration has negligible effect on the extent of inhibition. Fig. 19 shows graphically the effect of amino acids on arginase, residual enzyme activity times inhibitor concentration being plotted against arginine concentration (see p. 167 for derivation of relation).

In Fig. 19 we can see that ornithine, one of the reaction products, inhibits arginine breakdown in an apparently competitive manner. Consideration of the equilibrium of this reaction shows that either of the reaction products could act in this way by preventing dissociation of the enzyme-arginine complex, the extent of breakdown being obviously proportional to the concentrations of the various reactants. The inhibition of enzymic reactions by excess of one reaction-product is a fairly general effect. It may be encountered, for example, in bacterial suspensions to which a large excess of

some metabolite has been added. It is often misinterpreted as indicating that the metabolite is inhibitory *per se*, and erroneous theories have sometimes been based on such observations.

The foregoing account of enzyme inhibition has tended to over-simplify the phenomenon for purposes of classification. The divisions between specific and non-specific inhibitors and

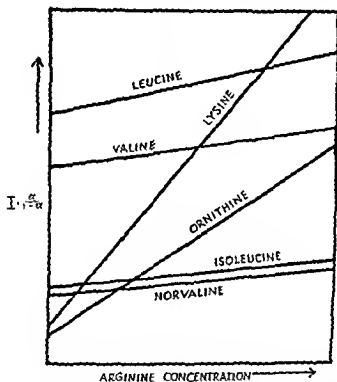


FIG 19.—Inhibition of arginase by *l*-amino acids. I = concentration of inhibiting amino acid, α = fractional activity, where $1 - \alpha$ = degree of inhibition. (Hunter and Downs, 1945.)

competitive and *non-competitive* are only valid when applied to one particular enzyme. An inhibitor may combine reversibly with a group at the active centre of one enzyme and show the characteristics of competitive inhibition, while with another enzyme it may attack a chemically similar group situated outside the active centre and will be classed as a non-competitive inhibitor. This would occur if the particular grouping which combined with the inhibitor was essential in

both cases but was concerned in combination with substrate or coenzyme only in the first case. The work of Hellerman and his co-workers on atabrin and quinoline bases as enzyme inhibitors suggests that all these compounds combine with similar groups in different enzymes, the resulting inhibition varying in type with the enzyme in question (Hellerman, Lindsay and Bovarnick, 1946). Any enzyme inhibited by one of these compounds was found to be inhibited by the whole group, the order of effectiveness in the group being similar for different enzymes. The enzymes *d*-amino acid oxidase, diaphorase, lactic dehydrogenase, pancreatic lipase and catalase were all inhibited by atabrin, plasmoquine, quinine and various non-antimalarial quinolines. The inhibition of *d*-amino acid oxidase by quinine was found to be a true competitive inhibition with respect to the coenzyme, flavin adenine dinucleotide; while with diaphorase, non-competitive inhibition was reported. Atabrin showed true competitive inhibition with pancreatic lipase, but its effect on *d*-amino acid oxidase was found to be not strictly competitive when investigated kinetically.

Inhibition by atabrin of flavoproteins, when first reported, was thought to be due possibly to a structural similarity between the atabrin and flavin molecules, since protection from inhibition could be afforded by the flavin-containing coenzyme (Wright and Sabine, 1944; Haas, 1944). However, the findings by Haas that atabrin also inhibited glucose-6-phosphate dehydrogenase, whose pyridine-nucleotide coenzyme could also protect against inhibition, suggested that this could not be the case. Quinine was also found to inhibit both these enzymes. Extension of the investigation by Hellerman and co-workers showed that these coenzyme antagonisms are not specific to atabrin, but are also shown by numerous quinolines, and cannot therefore be due to structural similarity with a portion of the coenzyme molecule. This was further stressed by the fact that all these compounds inhibit other totally unrelated enzymes. The one common property shown by all these inhibitors and the coenzymes is their basic nature. It is possible that they combine with certain acidic groups of the enzymes, and where such groups are concerned with

some metabolite has been added. It is often misinterpreted as indicating that the metabolite is inhibitory *per se*, and erroneous theories have sometimes been based on such observations.

The foregoing account of enzyme inhibition has tended to over-simplify the phenomenon for purposes of classification. The divisions between specific and non-specific inhibitors and

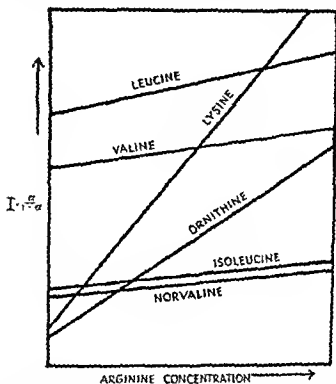


FIG. 19.—Inhibition of arginase by L-amino acids. I = concentration of inhibiting amino acid. a = fractional activity, where $1 - a$ = degree of inhibition. (Hunter and Downs, 1945.)

competitive and non-competitive are only valid when applied to one particular enzyme. An inhibitor may combine reversibly with a group at the active centre of one enzyme and show the characteristics of competitive inhibition, while with another enzyme it may attack a chemically similar group situated outside the active centre and will be classed as a non-competitive inhibitor. This would occur if the particular grouping which combined with the inhibitor was essential in

combination with coenzyme, a competition between coenzyme and inhibitor will occur.

We can see then that competitive inhibition is not necessarily confined to substrate analogues, and may not even be specific to one enzyme or class of enzymes. The danger of misinterpreting the action of an inhibitor as a result of testing on an insufficient number of enzymes is well illustrated in the case of the antimalarial drugs.

Kinetics of inhibition

A knowledge of the dissociation constant of enzyme-inhibitor complex is of great importance in assessing the potency of an inhibitor and the possibility of employing it *in vivo*. A study of the kinetics of enzyme inhibition provides a means for determining both this constant and, at the same time, the equally important dissociation constant of the enzyme substrate complex (Michaelis constant). It also provides mathematical proof, should it be required, for the differences between competitive and non-competitive inhibition.

The degree of enzyme inhibition caused by a non-competitive inhibitor is dependent solely on the amount of enzyme combined with the drug, and therefore the only equilibrium to be considered is that concerned with formation of enzyme-inhibitor complex.



Let I = concentration of inhibitor

e = initial concentration of enzyme

q = concentration of enzyme-inhibitor complex

K_I = dissociation constant of enzyme inhibitor complex

i = fractional inhibition

$$= \frac{q}{e}$$

α = fractional activity, where $1 - \alpha = i$.

Hunter and Downs (1945) substitute the term fractional activity (α) for $\frac{v}{v_0}$ in equation (9), which becomes

$$K_I = \frac{I \cdot K_s}{(K_s + S) \left(\frac{1}{\alpha} - 1 \right)}$$

or
$$I \cdot \frac{\alpha}{1-\alpha} = \frac{K_I}{K_s} (K_s + S)$$

$$I \cdot \frac{\alpha}{1-\alpha} = K_I + \frac{K_I}{K_s} S \quad . \quad . \quad . \quad (10)$$

Substituting C for $K_I + \frac{K_I}{K_s} S$, we get

$$I \cdot \frac{\alpha}{1-\alpha} = C \quad . \quad . \quad . \quad (11)$$

This equation is comparable with equation (7) obtained for non-competitive inhibition, except that, in this case, C is not a constant but is proportional to substrate concentration. The extent of inhibition is also proportional to the relative values of dissociation constants K_I and K_s . In other words, equation (10) shows us that the characteristic properties of competitive inhibition are variation of inhibition with substrate concentration and dependence on the relative affinities

of the enzyme for substrate and inhibitor. If $I \cdot \frac{\alpha}{1-\alpha}$ is plotted against S, the graph will be a straight line sloping upward from the axis of S (Fig. 20). Its intercept on the $I \cdot \frac{\alpha}{1-\alpha}$ axis is K_I and its slope is $\frac{K_I}{K_s}$, from which values

both K_I and K_s may be calculated. The term $I \cdot \frac{\alpha}{1-\alpha}$ represents a useful yardstick for relating the effects of different inhibitors. It is numerically equal to the concentration of inhibitor by which activity of a given enzyme is reduced to one-half of its original value.

Then, by the law of mass action,

$$S(e-p-q) = K_s p$$

$$I(e-p-q) = K_I q$$

eliminating q we get

$$K_I = \frac{I K_s}{S\left(\frac{e}{p} - 1\right) - K_s} \quad . \quad . \quad . \quad (8)$$

Let v_0 = velocity of enzymic reaction without inhibitor

v = velocity of enzymic reaction in presence of inhibitor

p_0 = concentration of enzyme-substrate complex in absence of inhibitor.

In each case the velocity of reaction is proportional to the concentration of enzyme-substrate complex.

$$\text{i.e.} \quad \frac{v_0}{v} = \frac{p_0}{p} \quad \therefore p_0 = \frac{v_0}{v} p.$$

Now, a value for p_0 has already been derived as $\frac{eS}{K_s + S}$ (p in equation (1) p. 150).

$$\therefore \quad \frac{v_0}{v} p = \frac{eS}{K_s + S}$$

$$\frac{e}{p} = \frac{v_0}{v} \cdot \frac{K_s + S}{S}$$

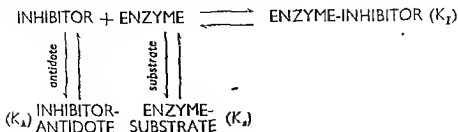
Substituting for $\frac{e}{p}$ in equation (8)

$$K_I = \frac{I \cdot K_s}{S\left(\frac{v_0}{v} \cdot \frac{K_s + S}{S} - 1\right) - K_s}$$

$$= \frac{I \cdot K_s}{\frac{v_0}{v} (K_s + S) - S - K_s}$$

$$K_I = \frac{I \cdot K_s}{(K_s + S)\left(\frac{v_0}{v} - 1\right)} \quad . \quad . \quad . \quad (9)$$

inhibitor complex is in equilibrium with the dissociated constituents according to the equation



At equilibrium, the extent of dissociation will depend on the dissociation constant (K_I) of the enzyme-inhibitor complex and will increase with increasing values of K_I . Equilibrium may be altered either by removal of enzyme by combination with additional substrate, or by removal of inhibitor through chemical combination with an antidote. The enzyme-inhibitor complex will then dissociate further in an attempt to restore the equilibrium, and some degree of reversal of inhibition will be effected. In the absence of antidote, the effectiveness of an inhibitor depends, as we have seen (equations 7 and 10), on the values of K_A and K_I .

Chemical combination of inhibitor with an antidote may provide an effective method of reversing enzyme inhibition. If the inhibitor-antidote complex is very insoluble, the reversal of inhibition is complete, since all the inhibitor is removed from solution. Such is the case in the reversal by hydrogen sulphide of the inhibition by heavy metals of "SH enzymes." Complete reversal could also be attained if the dissociation constant (K_A) of the inhibitor-antidote complex were very low compared with that of enzyme-inhibitor complex (K_I). Recent investigation on war gases has clearly demonstrated the dependence of toxic action upon the dissociability of poison-enzyme and poison-antidote complexes. The vesicant lewisite, and lachrymators such as chloracetophenone and bromobenzyl cyanide, were found to be powerful inhibitors of all "SH enzymes," i.e. low values of K_I (Dixon and Needham, 1946; Peters, Stocken and Thompson, 1945). Among a series of related lachrymators, the greatest degree of enzyme inhibition was obtained with those compounds which formed

Adequate study of enzyme inhibitors cannot be carried on without investigation of the kinetics of inhibition. This is now being realised to an increasing extent by workers in the field, who, however, often appear to fail to realise the value of the use of pure enzymes in their experiments. Much painstaking work on impure enzymes has subsequently been proved to be valueless when kinetic data were provided for the pure enzymes.

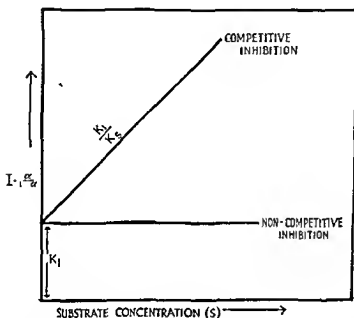


FIG. 20.—Characteristic graphs of competitive and non-competitive inhibition. I = inhibitor concentration, α = fractional activity, where $1 - \alpha$ = degree of inhibition. (Enables calculation to be made for values of K_I , dissociation constant of enzyme-inhibitor complex, and K_s , dissociation constant of enzyme-substrate complex.)

Kinetic treatment has been applied to the sulphonamide inhibition of growth of bacterial cells and its competitive reversal by *p*-aminobenzoic acid (Klotz and Gutmann, 1945). This enabled the dissociation constants (K_I) of the drug-enzyme complexes to be estimated.

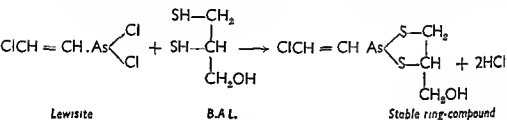
Reversal of inhibition

When inhibition of an enzyme is reversible, the enzyme-

of succinic dehydrogenase by malonic acid, we have a high affinity between substrate analogue and enzyme, the inhibitor/substrate ratio for 50 per cent. inhibition being as low as 1/50 (Potter and DuBois, 1943). This high affinity represents an exception, rather than the rule, and in most cases of competitive inhibition so far examined, K_i is found to be lower than K_1 . This might be expected in view of the high specificity shown by an enzyme for its natural substrate; it implies that reversal of drug inhibition can be effected, in certain cases, by increase in substrate concentration, an undesirable character in a chemotherapeutic drug. Kinetic data provided for *D*-amino acid oxidase (unfortunately on impure enzyme preparations), show that quinine inhibits the enzyme by competing with the coenzyme flavin adenine dinucleotide (Hellerman, Lindsay and Bovarnick, 1946). The ratio of the two dissociation constants K_1/K_i was about 1000, K_1 being about 4×10^{-4} and K_i 4×10^{-7} . With a quinine concentration of $10^{-3}M$, 61 per cent. inhibition was obtained with a coenzyme concentration of $0.4 \times 10^{-7}M$; when the coenzyme concentration was raised to $27.5 \times 10^{-7}M$ the degree of inhibition was reduced to 10 per cent. Here we see that because of the enormous difference between the dissociabilities of the complexes of enzyme with inhibitor and coenzyme, a very small amount of additional coenzyme in the reaction system largely eliminated the inhibition caused by a relatively high concentration of quinine.

Certain combinations between active centre and inhibitor may not be reversible. In this case, substrate or coenzyme can only protect against inhibition when added prior to the inhibitor, but the degree of inhibition will still be proportional to the concentration ratio. This condition has been found by Haas (1944) to occur in the inhibition by atobrin of cytochrome reductase and glucose-6-phosphate dehydrogenase. The reversibility of atobrin-enzyme combination appears to vary with different enzymes, since Hellerman reports that inhibition of pancreatic lipase by atobrin shows strictly reversible competition with substrate. With *D*-amino acid oxidase he suggests that the effect of atobrin might be explained by a

most stable addition products with thiols. Inhibition by lewisite of pyruvate oxidase or hexokinase could not be reversed by monothiols, such as cysteine or glutathione, which reacted with the poison to give compounds dissociating in dilute solution (K_A high). The dithiol 2:3-dimercaptopropanol (British anti-lewisite or B.A.L.) reacted with lewisite to form a highly stable non-dissociating ring compound (K_A low) and was completely effective in reversing the action of lewisite on pyruvate oxidase or other SH-enzymes (Stocken and Thompson, 1946; Whittaker, 1947; Barron *et al.*, 1947). B.A.L. was found to be effective not only in reversing the *in-vitro* inhibition of "SH enzymes" by lewisite, but also in



reversing the toxic and vesicant action of lewisite *in vivo* for at least an hour after contamination of the skin.

If K_A is equal to or slightly greater than K_I , fairly effective reversal of inhibition may be attained by the use of a large excess of antidote over inhibitor. The reversal by cysteine or glutathione of "SH inhibition" by arsenicals or mercurial compounds is an example of this type of reversal; reactivation of succinoxidase by glutathione after poisoning by *p*-carboxy-phenylarsenoxide required a glutathione concentration fifty times greater than that of the inhibitor (Barron and Singer, 1945a).

In competitive inhibition, where the inhibitor is antagonised by the substrate, we know that the relative values of K_I and the enzyme-substrate dissociation constant (Michaelis constant, K_s) play an important part in determining the efficiency of an inhibitor. An ideal competitive inhibitor would be one whose affinity for the enzyme is considerably greater than that of the substrate, otherwise the ratio of inhibitor/substrate concentrations would have to be high. In the case of inhibition

of succinic dehydrogenase by malonic acid, we have a high affinity between substrate analogue and enzyme, the inhibitor/substrate ratio for 50 per cent. inhibition being as low as 1/50 (Potter and DuBois, 1943). This high affinity represents an exception, rather than the rule, and in most cases of competitive inhibition so far examined, K_i is found to be lower than K_s . This might be expected in view of the high specificity shown by an enzyme for its natural substrate; it implies that reversal of drug inhibition can be effected, in certain cases, by increase in substrate concentration, an undesirable character in a chemotherapeutic drug. Kinetic data provided for *D*-amino acid oxidase (unfortunately on impure enzyme preparations), show that quinine inhibits the enzyme by competing with the coenzyme flavin adenine dinucleotide (Hellerman, Lindsay and Bovarnick, 1946). The ratio of the two dissociation constants K_i/K_s was about 1000, K_i being about 4×10^{-4} and K_s 4×10^{-7} . With a quinine concentration of $10^{-3}M$, 61 per cent. inhibition was obtained with a coenzyme concentration of $0.4 \times 10^{-7}M$; when the coenzyme concentration was raised to $27.5 \times 10^{-7}M$ the degree of inhibition was reduced to 10 per cent. Here we see that because of the enormous difference between the dissociabilities of the complexes of enzyme with inhibitor and coenzyme, a very small amount of additional coenzyme in the reaction system largely eliminated the inhibition caused by a relatively high concentration of quinine.

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slow irreversible combination superimposed on a strictly reversible reaction (Hellerman, Lindsay and Bovarnick, 1946). In the inhibition of SH-enzymes by heavy metals, increase in the concentration of metal may decrease the degree of reversal attained by addition of thiol compounds (Sumner and Myrbäck, 1930; Barron and Kalnitsky, 1947). This may be due to irreversible denaturation of the enzyme by the heavy metal.

Effect of inhibitors on living cells

The foregoing sections of this chapter have dealt in some detail with the inhibition of isolated enzymes. This is necessary, because any adequate consideration of mode of drug action in the living cell must be related to these facts. If, for example, a drug has a grouping which can combine with sulphydryl groups and its effect is reversed by an excess of cysteine, it is reasonable to assume that it is inhibiting some enzyme dependent for activity on free sulphydryl groups. The action of another drug might be reversed by a known metabolite in such a way that the ratio of drug to metabolite is constant for any given degree of inhibition; in this case the drug may be acting by competing with the metabolite for the enzyme whose substrate is that particular metabolite. These suppositions would be strengthened by investigating the effects of the drug on isolated enzymes of the types suggested by *in-vivo* experiments. However, a positive result from such experiments should not be taken as proof that the action on the particular enzyme is the *only* action of the drug *in vivo*, unless the importance of that enzyme in cell economy is known.

An indication of the importance of an enzyme to the cell may be obtained from a knowledge of the cellular concentration of enzyme and the rate at which it reacts with its particular substrate. A measure of this rate is given by the constant known as *Turnover Number*, which may be defined as the number of molecules of substrate (or coenzyme) which will undergo reaction with one molecule of enzyme in one minute when pH and substrate concentration are such that the

enzyme is working at its maximum velocity for the temperature under consideration. In the case of a respiratory enzyme, a knowledge of enzymic concentration and Turnover Number enables one to calculate the maximum fraction of total respiration which could pass through the pathway catalysed by that enzyme. The percentage inhibition of total cell respiration due to the action of the inhibitor on that pathway could then be calculated, and compared with the experimental value.

Unfortunately, enzymology has not progressed far enough for us to find in the literature all the data to enable such calculations to be made for most enzymes. The determination of the absolute amount of an enzyme in cells is a measurement which can be made with certainty only in a few cases, because of the difficulty of quantitative extraction from the cell. The difficulty in measuring Turnover Number is not so great, but in spite of this, insufficient data have been collected up to the present for calculation of Turnover Numbers of different enzymes when acting on *substrates actually present in the living cell*. McIlwain (1946) has estimated from available data the Turnover Numbers of various enzymes and also the amounts contained in a single bacterial cell. He concludes that certain enzymes, possibly associated with genes or cellular synthesis, must exist in concentrations of only one or a few molecules per cell; others exist in very much higher concentrations (see also Herbert and Pinsent, 1947).

In the case of cytochrome *c*, we are fortunate in having a protein whose activity and concentration can be measured in the intact cell by means of its absorption spectrum. This was first done for yeast by Haas (1934) by measuring with a photoelectric spectrophotometer the light absorption at $550\text{ m}\mu$ of a washed yeast suspension. This wave-length represents the position of the strongest visible absorption band of reduced cytochrome *c*, and its intensity gives a measure of the amount of reduced cytochrome *c* present at any given time. Comparison of the absorption at $550\text{ m}\mu$ of the yeast in a nitrogen atmosphere with that of a standard solution of reduced cytochrome *c* gave the concentration of cytochrome

THE BASIS OF CHEMOTHERAPY

as 1.43×10^{-5} m.M per ml. of yeast suspension. The rate of reduction of oxidised cytochrome *c* was determined by measuring, in the presence of cyanide, the rate of change of absorption of a fully-oxygenated suspension. Cyanide acts by inhibiting cytochrome oxidase, so the overall visible change was due only to conversion of oxidised cytochrome to the reduced form.

The velocity constant *K* for the reduction was calculated from the expression

$$K = \frac{1}{t} \ln \frac{C_0}{C}$$

where *t* = time in minutes.

*C*₀ = concentration of oxidised cytochrome at time *t* = 0.

C = concentration of oxidised cytochrome at time *t*.

K was found to be 4. This means that the volume of oxygen bound by cytochrome oxidase when acting through cytochrome *c* would be

$$4 \times \frac{22,400}{4} \times 1.43 \times 10^{-5} = 0.32 \text{ mm.}^3 \text{ O}_2 \text{ per ml. of cell sus-}$$

pension per minute, since 1 mol. of cytochrome is equivalent to $\frac{1}{4}$ of mol. of oxygen (p. 52). Manometric determination of oxygen consumption of the same yeast suspension gave a value of 0.34 mm.³ O₂ per ml. of cell suspension per minute. This shows that, under the conditions of the experiment, practically all the respiration of yeast passed through the cytochrome oxidase-cytochrome *c* system, and that the inhibitory effect of cyanide could be fully accounted for by its inhibition of cytochrome oxidase.

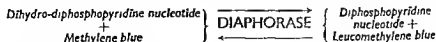
Having evidence that cytochrome is capable of transporting all the hydrogen which combines with oxygen in yeast respiration, Warburg (1934) calculated the Turnover Number of cytochrome from the cytochrome content and the oxygen uptake of the cells. The value for yeast worked out at 4000. Keilin (1940) calculated the Turnover Number of cytochrome *c* in yeast by a different method and obtained a value of 3850. It is interesting to compare these values obtained for intact cells, with the figure of 1420 given by Keilin for a cell-free

colloidal system containing the complete cytochrome system and succinic dehydrogenase. The much lower figure for the cell-free system indicates, as Keilin points out, "that the great efficiency of catalytic systems within living cells is due to a high structural organisation responsible for the proper spatial distribution and the most favourable molecular orientation of all components of the system." Methods have not yet been developed by which Turnover Numbers of most other enzymes can be measured in the intact cell, and it is probable that any value found *in vitro* represents a figure considerably below the *in-vivo* figure.

Negelein and Wulff (1937) provide data showing that *in vitro* one molecule of alcohol dehydrogenase can reduce at least 1800 molecules of pyridine nucleotide per minute. As far as Turnover Number is concerned, concentration of pyridine nucleotide in the living cell is highly misleading, since nucleotide coenzymes usually occur in large excess over the corresponding dehydrogenase proteins (Schlenk, 1942). Working with nicotinamide-deficient *Proteus vulgaris* produced by growth in low concentrations of nicotinamide, Morel (1941) estimated the concentration of nicotinamide in the cells when they first showed symptoms of nicotinamide deficiency. At this stage it is probable that all the coenzyme present was used for hydrogen transport. Measurement of the reducing power of such cells for methylene blue in the presence of glucose, gave a Turnover Number for nicotinamide dehydrogenases oxidising glucose *in vivo* as 600. As pointed out by Morel, it is unlikely that all hydrogen transport is mediated by the nicotinamide coenzymes, so that the figure given is a maximum for the conditions used. The value is considerably lower than that given by Negelein and Wulff for alcohol dehydrogenase, but this is to be expected, since the value arrived at by Morel represents an overall figure for depleted cells and for a whole group of dehydrogenases, some of which may have much lower Turnover Numbers. *In vivo*, moreover, there is no guarantee that at each stage in a series of linked dehydrogenations, each enzyme will be saturated with the appropriate substrate.

The Turnover Number of a flavoprotein enzyme in living *Lactobacillus delbrückii* was calculated by Warburg (1934) from unpublished figures obtained by Haas. This organism normally grows under anaerobic conditions; it has no cytochrome or other hæme pigments and is not affected by cyanide; in the presence of oxygen, however, it takes up oxygen and produces hydrogen peroxide. Haas observed a visible absorption band at 460 m μ under aerobic, but not under anaerobic, conditions, and concluded it was due to a flavoprotein. The rate of oxidation of the flavoprotein was calculated by observing anaerobically appearance of the band after addition of methylene blue. The corresponding oxygen uptake due to this enzyme was calculated to be 1.2 mm.³ O₂ per ml. suspension per minute, while the observed oxygen uptake was 1.0. Warburg concluded that all respiration of this organism, observed when it is kept under aerobic conditions, can pass through a flavoprotein. The Turnover Number for the enzyme was calculated to be 30. This is a very low value for a respiratory enzyme, but since the organism does not normally exist aerobically we may infer that the flavoprotein is not playing its normal role under these circumstances. A valuable extension of this work would be a determination of the Turnover Number of the flavoprotein under anaerobic conditions with no artificial hydrogen acceptor.

The flavoprotein diaphorase has been found to have *in vitro* a Turnover Number of 8000 when it is transferring hydrogen in the following system (Straub, Corran and Green, 1939; Straub, 1942):—



Although this value was not determined with the natural hydrogen acceptor of diaphorase, since it is unknown, there is evidence that this reaction rate is of the same order as in the intact cell. Unfortunately there are no figures available for the diaphorase content of cells, so that the proportion of respiration passing through diaphorase cannot be estimated.

The position is different with regard to cytochrome reductase, the other known flavoprotein concerned in hydrogen transport from pyridine nucleotide dehydrogenases to cytochromes. Here, in the case of yeast at least, a figure for its concentration has been given (Haas, Horecker and Hogness, 1940), and its Turnover Number has been estimated as 300 to 500 (Green, 1941). A Turnover Number of about 400 would seem to be a reasonable figure to use in an attempt to estimate the part played by this enzyme in respiration of bakers' yeast at 28°.

The rate of respiration of yeast expressed as respiratory coefficient, Q_{O_2} , is 60-80 at 28° (Q_{O_2} = mm.³ of oxygen used per mg. dry weight per hour). This means that 1 kg. dry weight of yeast takes up 0.045 gm. mol. of oxygen per minute. According to our calculation, 1 mol. of cytochrome reductase can in one minute transfer 400 mols. of hydrogen, i.e. can reduce 200 mols. of oxygen. The molecular weight of the enzyme is 75,000, and 1 kg. dry yeast contains 0.6 g. of enzyme, i.e. $\frac{0.6}{75,000}$ gm. mol. Therefore, number of gm. mols.

of oxygen taken up per minute by 1 kg. of yeast through cytochrome reductase = $\frac{0.6 \times 200}{75,000} = .0016$. This shows that

only $\frac{.0016}{.045}$, i.e. 3.5 per cent., of the total oxygen uptake of yeast

can be carried on by means of the glucose-6-phosphate dehydrogenase-cytochrome reductase system if this is the only system in which cytochrome reductase plays a part. Our knowledge of cellular metabolism is still so slight that we are unable to say whether cytochrome reductase acts as hydrogen acceptor to any enzyme other than glucose-6-phosphate dehydrogenase. Neither are we able to estimate the importance in normal aerobic respiration of this practically unknown route of carbohydrate oxidation, which is not the normal anaerobic glycolytic pathway about which more is known (pp. 68 and 72).

It is, however, instructive to examine the type of information we can obtain from these calculations in the

unlikely circumstances that all our assumptions are correct. We may say that any inhibitor acting exclusively on the glucose-6-phosphate dehydrogenase cytochrome reductase system would reduce respiration of yeast by 3.5 per cent. In the present state of knowledge, it is impossible to say whether an inhibitor acts only on one enzyme, but we may examine inhibitors known to act on the cytochrome reductase system

TABLE 11

Effect of inhibitors on isolated respiratory enzymes and on respiration of intact cells

System Studied	Per cent. Inhibition by		
	$10^{-3}M$ 2:4-dinitro-o-cyclohexyl phenol	$5 \times 10^{-4}M$ Atebrin	$5 \times 10^{-4}M$ Quinine
Glucose-6-phosphate } Dehydro- TPN } genase	90	78	0
TPN } Cytochrome Cytochrome c } reductase	70	73	14
Cytochrome c } Cytochrome oxidase Oxygen }	0	40	17
Respiration of bakers' yeast	93	-	0 (17 per cent. inhibition by $1.3 \times 10^{-4}M$) *
Respiration of malaria parasite	..	80 †	26 †

Figures from Haas (1944), except for * Rona and Grassheim (1923),

† Fulton and Christophers (1938).

and compare their effects on the isolated enzyme and on cellular respiration. Haas (1942) found that 2:4-dinitro-o-cyclohexylphenol has an inhibitory effect on cytochrome reductase in concentrations of $0.001M$; the same concentration also inhibited glucose-6-phosphate dehydrogenase but not cytochrome oxidase (see Table 11). We have to assume that cytochrome reductase is the only hydrogen carrier acting between glucose-6-phosphate dehydrogenase and cytochrome,

and therefore inhibition of either enzyme will have the same overall effect on respiration. We have calculated that this effect should be a 3.5 per cent. reduction of respiration. Haas found that $\cdot 001M$ 2:4-dinitro-*o*-cyclohexylphenol reduced respiration of yeast by 93 per cent., which suggests to us that the phenol also inhibits some other respiratory enzymes.

Experiments were also carried out by Haas (1944) on the effect of the antimalarial drugs atabrin and quinine on the enzymes involved in the oxidation of glucose-6-phosphate; these are compared in Table 11 with results of Rona and Grassheim (1923) and Fulton and Christophers (1938) on respiration of yeast and the malaria parasite. The concentrations used were of the same order as those occurring in the blood stream after administration of therapeutic doses. The results indicate that atabrin has a far greater inhibitory effect both on total cell respiration, and on the respiratory enzymes investigated, than has quinine. Haas interprets his results as showing that, among the known components of the respiratory system, only cytochrome reductase and glucose-6-phosphate dehydrogenase need be considered as possible points of interference by atabrin in the malaria parasite. This can only apply if the whole respiration goes through the cytochrome reductase pathway. Little is known of the respiratory mechanism of the malaria parasite, which seems, however, to conform to the general scheme of carbohydrate metabolism (Bovarnick, Lindsay and Hellerman, 1946 *a* and *b*; Evans, 1946; Speck and Evans, 1945*a*). The importance of the cytochrome reductase system is quite unknown, and Haas was unable to estimate the concentration of cytochrome reductase in parasites. Therefore Haas' assumption is unjustified, particularly as he himself shows that cytochrome oxidase, a very important respiratory enzyme, is inhibited by 40 per cent., a result confirmed by Hellerman, Bovarnick and Porter (1946).

Work by Hellerman, Lindsay and Bovarnick (1946) has shown that therapeutic concentrations of atabrin and quinine inhibit many other enzyme systems and may be regarded as fairly general enzyme poisons. The site of their attack on the living malaria parasite cell is therefore even more obscure,

particularly as many non-antimalarial quinolines were also shown to be effective enzyme inhibitors. However, with parasites initially depleted of glucose, the respiration resulting from addition of glucose is inhibited 75 to 90 per cent. by $0.001M$ atebirin; this inhibition can be reversed by adenylic acid or adenosine triphosphate in a manner suggesting competition. Quinine and plasmoquine had similar effects, and in all cases the inhibitory concentrations had no effect on cells not initially deprived of glucose (Bovarnick, Lindsay and Hellerman, 1946b). This suggestion that utilisation of adenosine triphosphate is inhibited by antimalarial drugs agrees with the finding of Speck and Evans (1945b) that atebirin inhibited hexokinase more strongly than any of the other known enzymes of carbohydrate metabolism. The possibility cannot be excluded that in all these cases combination occurred between basic drug and the acidic adenosine triphosphate, so that the drug was having no direct effect on the enzyme.

It must now be evident that there is great need for quantitative data on the amounts of various enzymes present in different micro-organisms and tissues, and on the Turnover Numbers of the reactions catalysed by these enzymes *in vitro*. Until such data are available, attempts to prove on a quantitative basis that a particular drug owes its activity to inhibition of a particular enzyme are of doubtful validity. Such attempts do, however, serve a useful purpose in indicating in which direction more knowledge must be sought, and in suggesting other methods of quantitative attack on the same problem based on the effect of drug antagonists (see Chapter V).

Reduction of respiration of an organism probably implies that an inhibitor is acting on one or more of the enzymes concerned with carbohydrate breakdown. Some indication of the site of action in the intact cell may sometimes be obtained by demonstration of accumulation of an intermediate product normally metabolised by the cell. Such a case is the strong inhibition of carbohydrate breakdown by fluoride, in which there is an accumulation of 2-phosphoglyceric acid (see p. 161); here it is possible to say that the major effect of

fluoride is on enolase which acts on phosphoglyceric acid. Inhibition of oxidation or fermentation of one carbohydrate, for example glucose, but not of some of its normal breakdown products such as pyruvate or lactate, may suggest that the site of inhibition is on the pathway between glucose and pyruvate. A change in anaerobic breakdown product may also indicate blockage of one method of breakdown; for example, if a fermenting organism which normally produces mostly acetic acid from added pyruvic acid produces lactic acid under the influence of an inhibitor, one may surmise that the path from pyruvic to acetic acid is blocked, but that the cell is able to utilise an alternative pathway for energy production (see p. 267 for specific examples).

This use of alternative metabolic pathways under the influence of enzyme inhibitors may play an important part in the overall effect of inhibitors on cells. For example, two organisms may react differently to the same inhibitor because one may have an alternative pathway available and so can bypass the inhibited step, while the other will suffer some adverse effect through inability to utilise another pathway. The forcing of a reaction through an alternative pathway can also be imagined to be harmful to an organism, since the alternative route may not be a complete substitute for the normal reaction.

Work by Hotchkiss (1944) on the antibiotic gramicidin, suggests that it may act on micro-organisms by preventing normal energy exchange through stimulating an abnormal non-phosphorylative type of carbohydrate breakdown. Gramicidin, like many other chemotherapeutic agents, has a bacteriostatic rather than a bactericidal action at the concentration used therapeutically. This could result from the inability of the poisoned cell to utilise energy to force synthetic reactions required for growth and cell division. Hotchkiss found that gramicidin, dinitrophenol and azide all increased the rate of respiration of *Staph. aureus* but inhibited the uptake of inorganic phosphate normally associated with respiration. Growth of yeast is not so readily inhibited by gramicidin as is that of *Staph. aureus*; yeast is, however, susceptible to

inhibition by dinitrophenol, and here too, uptake of inorganic phosphate and synthesis of polysaccharide were inhibited by this drug. Dinitrophenol and azide probably prevent utilisation of metabolic energy for synthetic processes by inhibiting certain energy-rich phosphate transfers without inhibiting carbohydrate breakdown (Clifton and Logan, 1939; Winzler, Burk and du Vigneaud, 1944; Spiegelman, Kamen and Dunn, 1946). The fate of "labelled" phosphorus in normal yeast was investigated by Spiegelman and Kamen (1946), who showed that during protein synthesis there was a fall in nucleoprotein phosphorus. No such fall occurred when fermentation was allowed to proceed in the absence of a source of nitrogen, when there was no growth or protein synthesis. Under conditions otherwise suitable for protein synthesis, dinitrophenol and azide prevented the fall in nucleoprotein phosphorus (review, McElroy, 1947).

The importance of phosphorylation as a mechanism for energy storage and transfer has already been stressed. So far as we know, energy-rich phosphate bonds are the main energy store available for the forcing of desirable endergonic reactions, and any substance capable of preventing the formation or utilisation of phosphate bonds may prevent cell synthesis. Spiegelman and Kamen suggest that nucleoprotein phosphorus may be intimately concerned with cell synthesis, so that interference in its metabolism may prevent growth. Penicillin also seems to act by preventing cell synthesis rather than by interference with the oxidative energy-yielding mechanisms, and it may be significant that nucleic acid metabolism is susceptible to inhibition by this drug (Krampitz and Werkman, 1947). The passage of glutamic acid across the cell wall of *Strep. faecalis* is also dependent on a supply of energy and is inhibited by penicillin. Gale and Taylor (1946b, 1947b) suggest that this may be the primary site of penicillin inhibition (see p. 272 for full discussion).

Since many other chemotherapeutic drugs prevent the growth of susceptible organisms rather than kill them outright, it is evident that they could also act by preventing synthetic rather than degradative reactions. This could be

effected either by inhibition of energy-producing reactions or by inhibition of synthetic processes themselves. The point is illustrated by the following example: growth of *Escherichia coli* in a synthetic ammonium chloride medium was accompanied by uptake of ammonium ion from the medium. This fixation of nitrogen required an oxygen consumption about 55 per cent. above that of resting cells. The resting respiration was scarcely affected by concentrations of sulphathiazole which completely inhibited growth, but the additional respiration associated with nitrogen fixation and cell synthesis was as susceptible to inhibition by sulphathiazole as was growth itself (Armstrong and Fisher, 1947; Fisher and Armstrong, 1947). These experiments do not indicate that sulphathiazole inhibits growth by inhibition of a sulphonamide-sensitive respiratory system associated with growth; they simply indicate a trap for the unwary—confusion of cause and effect. There is little doubt, as we shall show, that the primary site of sulphonamide inhibition is in the conversion of *p*-aminobenzoic acid to pteroylglutamic acid. The degree of inhibition of sulphonamide-sensitive respiration is probably a measure of the lessened need of the cell for exergonic oxidative reactions when its endergonic synthetic reactions are inhibited. As we pointed out previously, very little is known about these synthetic reactions, so our lack of direct knowledge on the mode of action of chemotherapeutic drugs is not surprising.

As far as we know, the main energy-producing pathways employed by most animals and heterotrophic micro-organisms are similar. This may be attributed to the fact that both forms of life derive most of their energy from the carbohydrates, and that differentiation during evolutionary development has been more concerned with change in synthetic pattern than with change in energy source for building that pattern. Chemotherapy is concerned with destruction of invading micro-organisms in the tissues of the host; this means that a successful chemotherapeutic drug attacks the micro-organism but not the host. This implies that the enzymes in the micro-organism which are inhibited by the drug may have different essential groups from those in the

host; alternatively, the susceptible enzymes may be either absent from the host tissues to which the drug has access, or of relatively less importance to the host. A successful chemotherapeutic drug, *i.e.* one that is completely non-toxic to the host, is therefore unlikely to inhibit strongly any part of carbohydrate breakdown common to both host and infective agent, unless an effective alternative path is available to the host. A completely rational approach to chemotherapy could only be achieved after acquisition of full knowledge of all the enzyme systems of animals and micro-organisms. This is a goal for the future. At present we can only examine the effects on organisms and isolated enzymes of our known chemotherapeutic drugs, and from a knowledge of the principles of enzyme inhibition described in this chapter, make attempts at guessing their mode of action.

CHAPTER V

DRUG ANTAGONISM

act. of base

SINCE enzyme inhibition is often a reversible process, it is not surprising that the growth-inhibitory action of drugs on living cells can frequently be reversed by addition to the drug-cell system of a third component which can bring about removal of the drug from its site of action. The simplest of all examples of drug antagonism, and one which is of such daily occurrence that its nature is generally ignored, is the antagonism between hydroxyl and hydrogen ions. Growth of a micro-organism in the richest media is prevented by the addition of excess alkali (drug), but the antibiotic action of alkali may be antagonised by addition of a suitable quantity of acid (antagonist), and cell growth is resumed, provided, of course, that the micro-organism has not been left for too long in the alkaline medium so that irreversible denaturation of cellular protein has occurred.

Antagonism may be direct, in that the antagonist combines chemically with the drug and forms a physiologically inactive drug-antagonist complex, or it may be indirect, in that no chemical interaction between drug and antagonist is possible but each is capable of displacing the other from its biological point of action. Several examples of such indirect antagonism in isolated enzyme systems have been described in the previous chapter as competitive inhibitions. The conditions under which competitive inhibition can be expected have been described and criteria for the competitive nature of an inhibition have been laid down (Chapter IV).

It will be remembered that competitive inhibition has been found to occur when an enzyme system is treated with a compound which is structurally similar to a natural substrate and which can therefore "fit" protein. All essential metabolic coenzymes, prosthetic groups, activators or building blocks

are in the protein structure some "fit"
their particular electronic configuration. Any substance, made available to the living cell, which penetrates the cell wall and is closely similar in electronic configuration to an essential metabolite (organic or inorganic), will be able to be caught up in the metabolic wheel at the point specifically designed to accommodate the related metabolite. If the structure of the metabolite analogue is such that it can undergo chemical changes similar to those undergone by the natural metabolite, but at a slower rate, then the living cell may utilise the analogue as an unsatisfactory substitute, and grow at a reduced rate limited by the Turnover Number of the modified enzyme system. If the metabolite analogue "fits" the enzyme but cannot undergo conversion to a functional form, then it may act as an enzyme inhibitor and hence as a growth inhibitor. The nature of its mode of action will be indicated by the capacity of the natural metabolite to act as an antagonist in a competitive manner.

Some confusion of thought has arisen from the above argument. Although a metabolite analogue may act as a growth inhibitor by displacing the natural metabolite, it does not follow that every substance capable of reversing the

role of the antagonist, even when the drug-antagonist relationship follows all the laws of competitive inhibition. Evidence for the metabolic function of a drug antagonist must come from studies on metabolism, rather than from studies on drug antagonism.

The drug antagonisms of classical pharmacology were well recognised long before the subject became of immediate interest in the biochemical interpretation of chemotherapy; it is not possible to give a detailed account of the work here, and the monograph by A. J. Clark (1937) should be consulted as a guide to this field. "Therapeutic interference" was the term used by Browning to describe the reduction in trypano-

cidal action which could be caused by injection of a second drug after feeding of a trypanocidal drug (see p. 230). Not until the sulphonamides assumed a leading place in chemotherapy and their mode of action was subjected to intensive study, did therapeutic interference and drug antagonism begin to shed light upon the enzymic interpretation of drug action.

Sulphonamides and p-aminobenzoic acid

The reversal of the bacteriostatic effect of sulphonamides by peptone was noted by Lockwood (1938). In the following

TABLE 12

Concentration of antagonist required to reverse growth inhibition of Strep. haemolyticus caused by sulphanilamide

Concentration of sulphanilamide ($M \times 10^{-3}$) (a)	MI of extracted antagonist ($\times 10^{-1}$) (b)	Ratio b/a	Concentration of p-aminobenzoic acid ($M \times 10^{-7}$) (c)	Ratio c/a $\times 10^{-4}$
0.303	0.016	5.3	0.58	1.92
1.515	0.08	5.3	2.01	1.02
7.575	0.4	5.3	14.54	1.92

(Woods, 1940.)

year, Stamp (1939), in seeking for other sulphonamide antagonists, found that a concentrated extract from hæmolytic streptococci was about a hundred times more active than peptone. Stamp suggested that his substance might be an essential metabolite for bacteria and an essential part of an enzyme system which was inhibited by sulphanilamide. Green (1940) extracted from culture media filtrates of *Brucella abortus*, and from the organism, a factor which reversed the bacteriostatic action of sulphanilamide. He suggested, also, that this factor acted by stimulating some enzyme system in the bacterial cell which was inhibited by sulphanilamide. Soon afterwards, Woods (1940) showed that a sulphanilamide antagonist, prepared in much the same way as Stamp's

are in the last analysis substrates, in the sense that some protein structure in the cell is specifically designed to "fit" their particular electronic configuration. Any substance, made available to the living cell, which penetrates the cell wall and is closely similar in electronic configuration to an essential metabolite (organic or inorganic), will be liable to be caught up in the metabolic wheel at the point specifically designed to accommodate the related metabolite. If the structure of the metabolite analogue is such that it can undergo chemical changes similar to those undergone by the natural metabolite, but at a slower rate, then the living cell may utilise the analogue as an unsatisfactory substitute and grow at a reduced rate limited by the Turnover Number of the modified enzyme system. If the metabolite analogue "fits" the enzyme but cannot undergo conversion to a functional form, then it may act as an enzyme inhibitor and hence as a growth inhibitor. The nature of its mode of action will be indicated by the capacity of the natural metabolite to act as an antagonist in a competitive manner.

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relationship between *sulphanilamide* and *P.A.B.A.* which is the substrate for the enzymic reaction in question." Woods also suggested that the *sulphonamide* resistance of some organisms might be sufficient to meet the needs of the organism.

synthesis, rather than utilisation, of *P.A.B.A.* is disposed of by the existence of a competitive relationship between *sulphanilamide* and *P.A.B.A.* If synthesis, not utilisation, of *P.A.B.A.* were inhibited, the addition of a threshold quantity of *P.A.B.A.* to the medium would meet the needs of the organism and permit growth independently of the amount of *sulphanilamide* present; such is not the case, and increase in concentration of *sulphanilamide* has to be met by a corresponding increase in *P.A.B.A.*

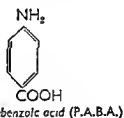
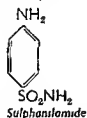
The anti-sulphonamide action of *P.A.B.A.* is evident *in vivo* as well as in culture media (Selbie, 1940). Mice infected with lethal amounts of *Strep. haemolyticus* may be protected by a dose of *sulphanilamide* which has no protective effect if *P.A.B.A.* is administered simultaneously.

The suggestion as to the nature of the *sulphonamide* antagonist extracted from micro-organisms was confirmed by the isolation of *P.A.B.A.* from yeast extracts (Rubbo and Gillespie, 1940; Blanchard, 1941). *P.A.B.A.* was also found to exist in a bound form as a *glutamic acid* peptide (Ratner, Blanchard, Coburn and Green, 1944), a particularly interesting observation in view of the recent elucidation of the structure of folic acid (p. 210) (Angier *et al.*, 1946).

It must be emphasised that the original observations of Woods on the antagonistic action of *P.A.B.A.* do not constitute evidence for the metabolic role of the antagonist. Evidence for the metabolic function of *P.A.B.A.* had to be sought after the suggestion of its possible metabolic importance had been made. It was soon shown to be a growth factor for *Clostridium acetobutylicum* (Rubbo and Gillespie, 1940), and later for *Acetobacter suboxydans*, *Lactobacillus arabinosus*, *Corynebacterium diphtheriae* and for certain strains of yeast. These observations naturally stimulated interest in and acceptance

concentrate, contained an amino derivative of an aromatic carboxylic acid. This antagonist was also shown to be obtainable from various plant and animal tissues. It antagonised sulphanilamide in a competitive manner, since the ratio of the amount of antagonist to sulphonamide was constant for various sulphonamide concentrations (see Table 12).

Competition between substances of closely related chemical structure in enzymic reactions was already well recognised, and suggested to Woods that the active fraction of his extract was closely related in chemical structure to sulphanilamide. Accordingly, he tested a series of compounds related to sulphanilamide for antagonistic action, and found that *p*-aminobenzoic acid at a concentration of 1.2 to $5.8 \times 10^{-8} M$ was sufficient to reverse the inhibition caused by $3.03 \times 10^{-4} M$ sulphanilamide. As with yeast extracts, there was a constant ratio between the concentration of sulphanilamide and the concentration of *p*-aminobenzoic acid required to reverse the inhibition (Table 12).



Of sixteen compounds related to *p*-aminobenzoic acid which Woods tested, only two, novocaine and *p*-hydroxylaminobenzoic acid possessed antagonistic action comparable to *p*-aminobenzoic acid; both these compounds might be readily convertible to *p*-aminobenzoic acid by familiar biological reactions. From this evidence, Woods felt justified in suggesting that the "natural" antagonist occurring in yeast and bacterial extracts which gave reactions for an aromatic-amine acid was in fact *p*-aminobenzoic acid (P.A.B.A.). He further suggested that P.A.B.A. is an essential metabolite and that "the enzymic reaction involved in the further utilisation of P.A.B.A. is subject to competitive inhibition by sulphanilamide and that this inhibition is due to a structural

having a structure essentially similar to P.A.B.A. are antagonised by P.A.B.A. in their antibiotic effect on most living organisms. The essential structure may be defined as a free aromatic amino group in the para-position to a sulphonic acid or other acidic group. The conversion of the sulphonic acid to an amide enhances activity, particularly when the amide group derives from a suitable heterocyclic base. The formulæ of some of the clinically useful sulphonamides are given.

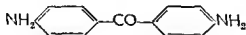
Compounds of related structure such as marfanil,



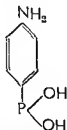
in which the primary amino group is not aromatic, may be bacteriostatic, but are not antagonised by P.A.B.A. On the other hand, aromatic amines in which the sulphonic acid radical is replaced by other acidic radicals such as AsO_3H_2 , $\text{CO}\cdot\text{Ph}$, PO_2H_2 , or SH as in atoxyl, diaminobenzophenone, aminobenzophosphonous acid or aminothiophenol are bacteriostatic for some organisms, and this bacteriostasis is reversed by P.A.B.A. (see Northey, 1940; Schmidt and Sesler, 1946; Kuhn, Möller, Wendt and Beinert, 1942; Kuhn, Möller and Wendt, 1943; Klotz and Morrison, 1947, for fuller discussion).



Atoxyl



4 : 4-Diaminobenzophenone

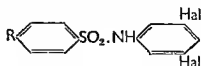


Aminobenzophosphonous acid



Amino-thiophenol

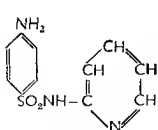
Halogenated sulphonamides of the general type



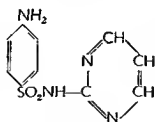
are bacteriostatic even if R is not an aromatic amino group, and are not necessarily antagonised by P.A.B.A. (Goetchius

of Woods' theory, but it was not possible to demonstrate the essential metabolic function of P.A.B.A. for all organisms which were sensitive to sulphonamides. Indirect evidence for the essential nature of P.A.B.A. was provided by recognition of its general distribution in animal, plant and bacterial cells. In many products, a considerable proportion was present in the "bound" form, and only released by autolysis or hydrolysis. To meet the difficulty of estimation of the very small quantity of P.A.B.A. involved, an ingenious microbiological method was introduced by Mirick (1943). A strain of soil bacillus, isolated by growing on P.A.B.A. as the only source of carbon and nitrogen, produced an enzyme specifically adapted to oxidise P.A.B.A. A particularly striking confirmation of the essential metabolic role of P.A.B.A. was obtained by isolation of an X-ray mutant strain of *Neurospora* for which P.A.B.A. was an essential growth factor. The normal strain did not require P.A.B.A., but apparently was capable of synthesising its own requirements. The mutant strain had lost this capacity, without at the same time losing the need for P.A.B.A. as a component of its metabolic system (Tatum and Beadle, 1942).

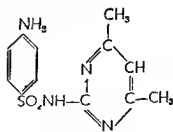
Before discussing other theories of sulphonamide action, it will be as well to summarise the agreed facts about the action of sulphonamides on living organisms. All sulphonamides



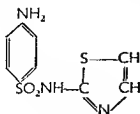
Sulphapyridine



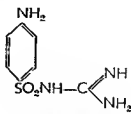
Sulphadiazine



Sulphamethazine



Sulphathiazole



Sulphaguanidine

in vitro but no more active *in vivo*. The anti-catalase theory of III
 Locke, Main and Mellon (1938)
hydroxylaminobenzenesulphonamid
as an inhibitor of catalase, the e

to be discarded because of the absence of complete competitive antagonism of hydroxylaminobenzenesulphonamide by P.A.B.A.

One theory of the relationship between sulphonamides and P.A.B.A., that of Sevag and his colleagues must, however, be considered in detail (Sevag and Shelburne, 1942b; Sevag, 1946). This theory is based on the premise that P.A.B.A. is not an essential metabolite but a non-toxic analogue, able to displace sulphonamides non-specifically from any enzyme surface without itself inhibiting to the same extent the normal action of the enzyme concerned. It also differs from the IV

respiratory enzymes, the sulphonamides are said to deprive
cells of the energy-yielding reactions, and so of the energy
necessary for cell division and growth. It will be noted that
 this theory involves two distinct sections: (a) the nature of the
competition between P.A.B.A. and sulphonamides, and (b) the
type of enzyme inhibited—a point left entirely open in the
 Woods' theory.

Sulphonamide inhibition of bacterial respiration was found to be proportional to sulphonamide inhibition of growth (Sevag and Shelburne, 1942a). Further, under suitable nutrient conditions, where organisms were able to respire but not to grow, respiration was inhibited to a lesser degree by sulphonamides than was the case with growing cells. P.A.B.A. reversed sulphonamide inhibition of respiration in low concentrations (6×10^{-3} to $6 \times 10^{-4}M$), but in higher concentrations (12×10^{-3} to $35 \times 10^{-3}M$) was itself inhibitory. These results were interpreted by Sevag as indicating that a sulphonamide-sensitive respiration existed, inhibition of which caused

in vitro but no more active *in vivo*. The anti-catalase theory of Locke, Main and Mellon (1938) assumed the existence of hydroxylaminobenzenesulphonamide at the site of action as an inhibitor of catalase, the enzyme responsible for the destruction of (and protection of the cell from) any hydrogen peroxide formed during metabolism. This theory also had to be discarded because of the absence of complete competitive antagonism of hydroxylaminobenzenesulphonamide by P.A.B.A.

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stoppage of growth; also that P.A.B.A. was not an essential metabolite but simply a less toxic chemical analogue of sulph

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1940; Dorfman and Koser, 1942). When the dysentery bacillus was grown in a synthetic medium deficient in nicotinamide and respiration was stimulated by addition of nicotinamide, this stimulated respiration was inhibited by sulphapyridine or sulphathiazole but not by sulphanilamide, sulphadiazine, sulphapyrazine or sulphacetamide. The inhibition was not reversed by P.A.B.A., but was prevented by nicotinamide, if it was added prior to the sulphonamide. In view of the isosterism between the pyridine and thiazole rings (Schmelkes, 1939; Tracy and Elderfield, 1940) the similar action of sulphapyridine and sulphathiazole was to be expected (see also p. 218).

✓ Sevag and his colleagues carried these observations further by showing that bacterial enzymes decarboxylating pyruvic acid (carboxylases) were partially inhibited by sulphonamides, and that su chemically related exerted the greatest I Mudd, 1942, 1945; Sovag, Henry and Richardson, 1945). Co-carboxylase antagonised in a competitive manner the inhibition by sulphathiazole of carboxylase activities of whole yeast, *Staph. aureus* or *Escherichia coli*. P.A.B.A. was able to reverse the inhibitory action of sulphathiazole on carboxylase activity of *S. aureus* and *E. coli*, despite the fact that in this reaction it could not possibly play the role of substrate. On the other hand, P.A.B.A. had no antagonistic effect on the inhibition of carboxylase by acetaldehyde. These results showed that P.A.B.A., in the particular case under examination, had a non-specific ability to protect an enzyme from the inhibitory effect of a sulphonamide. This non-specific antagonistic relationship between sulphanilamide and P.A.B.A. is also shown in a simpler physical system. The adsorption of

methylene blue by charcoal is inhibited by sulphanilamide ; in the presence of P.A.B.A., sulphanilamide loses its inhibitory action (Eyster, 1943).

Parallelism between sulphonamido structure and degree of inhibition of respiratory enzymes through competition with coenzymes has not been extended by more recent work (Altman, 1946). The enzyme (phenylacetate hydratase) was inhibited by sulphanilamide but to a lesser extent by sulphapyridine, sulphathiazole or sulphadiazine. The enzyme could be protected by the presence of either coenzyme (triphosphopyridine nucleotide) or substrate, but in their absence, sulphanilamide formed an irreversible complex. Moreover, P.A.B.A. exerted no protective effect

Since sulphonamides exert their therapeutic effect by preventing growth of micro-organisms, any satisfactory theory of their mode of action must be based upon results obtained from studies on bacterial growth. In general, Sovag's respiration studies were confirmed by experiments on growth, but these experiments have been criticised because of the high concentrations of sulphonamides used. A more serious difficulty is that several cases have been reported where effect of a sulphonamide on growth is not paralleled by its effect upon respiration. The inhibition of respiration of haemolytic streptococci by sulphanilamide is no greater than the inhibition of respiration of *Staph. aureus* by the same concentration of drug, although the growth of haemolytic streptococci is more readily inhibited than the growth of *Staph. aureus* (Wyss, Strandkov and Schmelkes, 1942). Moreover, the nicotinamide-stimulated respiration of dysentery bacillus was inhibited by sulphapyridine but not by sulphanilamide ; growth was, however, inhibited by sulphanilamide as well as by sulphapyridine. The inhibition of growth by sulphapyridine or sulphanilamide was completely antagonised by P.A.B.A., but the inhibition of respiration caused by sulphapyridine was not reversed by P.A.B.A. (Dorfman, Rice, Koser and Saunders, 1940 ; Dorfman and Koser, 1942). Additional difficulties are raised by other observations ; acetylation of sulphapyridine lowered its growth-inhibitory effect without lowering its effect

as an inhibitor of respiration. The growth of a strain of *Escherichia coli* rendered resistant to sulphonamides was inhibited to the extent of 50 per cent. by 0.0044M sulphanilamide, while in the parent strain growth was inhibited to the same extent by 0.00024M sulphanilamide; despite this difference in growth-sensitivity, the respiration of both strains was inhibited to the same extent by 0.04M sulphanilamide (Wyss, Strandkov and Schmelkes, 1942). Respiration of "P.A.B.A.-less" *Neurospora* mutants and of the normal parent strain was unaffected by all concentrations of sulphanilamide, although growth was inhibited in both cases (Tatum and Giese, 1946).

This lack of parallelism between the inhibitory actions of sulphonamides on growth and on respiration has its counterpart in the acridine series. Ferguson and Thorne (1946) found that with *Escherichia coli* the order of activity of several acridine derivatives in inhibiting growth was not the same as their order in inhibiting oxidation of various substrates. It appears that the bacteriostatic action of drugs is not dependent mainly on inhibition of oxidative energy-producing reactions; it is more likely that reactions closely connected with synthetic processes are inhibited (see p. 184). Tatum and Giese (1946) observed that germination of *Neurospora* conidia is much more sensitive to the inhibitory action of sulphanilamide than is the growth of actively-growing cultures. They suggest that in conidia, enzymes are present in low concentrations and active synthesis is required for growth; whereas in growing mycelia, the enzymes are already present in larger amounts.

Sevag's suggestion is that P.A.B.A. might be non-specific in its action and owe its sulphonamide-antagonistic action to its ability to displace sulphonamides from surfaces upon which they were adsorbed, without itself being an essential metabolite or playing any part in essential enzymic processes of the cell. While this point of view must be regarded as quite legitimate, there is absolutely no doubt that P.A.B.A. does play some vital function in growth and cellular metabolism. There is evidence also that in some cases sulphonamide-

resistant organisms do synthesise P.A.B.A. in greater amounts than their parent strains (Landy and Gerstung, 1944; Landy, Larkum, Oswald and Streightoff, 1943). P.A.B.A. is also unique in that it is capable of antagonising completely the bacteriostatic effect of many sulphonamides over a wide range of concentration; none of the respiratory coenzymes has a comparable effect. The P.A.B.A. reversal of inhibition of carboxylase activity caused by sulphathiazole is not invariably complete (Sevag, Henry and Richardson, 1945). The observation of Sevag that P.A.B.A. can itself act as an enzyme inhibitor and a growth inhibitor in high concentrations is not inconsistent with the known facts of enzymology, since in many cases when substrate concentration is increased beyond a certain point the substrate acts as an inhibitor.

Other metabolite analogues such as pyriethi amino, gluco-ascorbic acid, etc. (see p. 220), when fed to animals produce symptoms which can be ascribed to interference with the normal function of the related metabolite. Sulphathiazole does not produce symptoms of co-carboxylase deficiency in higher animals. The usual finding after feeding of sulphonamides to laboratory animals is inhibition of bacterial growth in the intestine with a resulting deficiency of factors believed to be obtained by animals from bacterial synthesis in the intestine, such as biotin and vitamin K (Daft and Sebrell, 1945); deficiency symptoms are relieved by feeding of these factors. The only clearly defined toxic reactions to large doses of sulphonamides in man are granulocytopenia and leucopenia. It is suggestive that folic acid seems to be particularly concerned with the reproduction of bone marrow cells, and that sulphonamides, which may prevent synthesis of folic acid, cause failure of bone marrow cell reproduction. Evidence for a relationship between sulphonamide inhibition and folic acid synthesis is discussed more fully in succeeding sections.

The evidence discussed so far would seem to leave the original suggestion of Woods that sulphonamides act in virtue of their similarity to an essential metabolite, viz. P.A.B.A., as the only satisfactory theory for the mode of action of these

drugs. Some sulphonamides do inhibit respiratory enzymes, but this may be a secondary rather than a primary action. *There is no reason to suppose that bacteriostatic agents always act on a single stage in the chain of enzymic reactions involved in cell metabolism; some sulphonamides may act on one stage only, others may be capable of inhibiting several.* The evidence collected by a number of investigators on the quantitative relationship between sulphonamide inhibition and P.A.B.A. antagonism does suggest, however, that all sulphonamides possessing a free primary aromatic amino group are caught up in cellular metabolism at, at least, one common point. Bradbury and Jordan (1942), from a study of the electrokinetic mobility of suspensions of *Escherichia coli* in dilute solutions of either sulphonamides or P.A.B.A., concluded that all the bacteriostatic sulphonamides and P.A.B.A. affected electrokinetic mobility in the same way, and were probably adsorbed in the same way by the cell; whereas inactive related compounds such as aniline and *m*-aminobenzene sulphonamide behaved quite differently. Fox and Rose (1942) found that although the bacteriostatic potency of various sulphonamides varied over a wide range, the amount of P.A.B.A. required to antagonise the minimal effective concentration (M.E.C.) of drug was constant (see Table 13).

TABLE 13

Minimum effective concentration of sulphonamides and amount of P.A.B.A. required to antagonise this concentration
(Fox and Rose, 1942)

	M.E.C. ($M \times 10^{-4}$)	Amount P.A.B.A. for Reversal of Bacteriostasis ($M \times 10^{-4}$).
Sulphanilamide	2500	0.3
Sulphapyridine	20	0.5
Sulphathiazole	4	0.5
Sulphadiazine	4	0.5

It is difficult to interpret such observations in any other light than that suggested above, namely, the identity of one primary site of action of all sulphonamides antagonised by P.A.B.A. Such quantitative studies, however, do not help to elucidate the finer point as to the nature of the system inhibited, although they have been extremely useful in

correlating structure with antibiotic action among sulphonamides (see Chapter VII). It is not possible at present to do more than guess at the nature of the enzyme system actually involved, because as pointed out in an earlier chapter, we are largely ignorant as yet concerning the synthetic processes going on in living cells.

Sulphonamide antagonists other than P.A.B.A. ✓

Further complexity has been added to the problem of sulphonamide action by the array of so-called secondary sulphonamide antagonists. In discussing these, it must be emphasised that were a single enzymic reaction of a living cell inhibited by a drug, the results would extend along a whole chain of inter-related enzyme systems. This would result in various aberrations of normal metabolism, each subject to further modification or restoration by addition of intermediate metabolites to the nutritive medium.

At least four general types of sulphonamide antagonist may be listed :— *non specific*

- (1) Essential metabolites which are displaced or replaced by sulphonamides, *e.g.* P.A.B.A.
- (2) Substances which, when added to a nutritionally poor medium, increase rate of growth and so mask sulphonamide inhibition in a non-specific way ;
✓ glucose may act in this way in suitable media.
- (3) Compounds which combine with sulphonamides and render them unavailable for bacteriostasis, *e.g.* proteins, urethane.
- (4) Metabolites normally synthesised by the cell in reactions secondary to, and dependent upon, a primary reaction which is inhibited by sulphonamides, *e.g.* methionine.

The first type of antagonist we have already discussed ; to the second group belong all those substances which cannot be shown to act in any specific way. When drug antagonism is observed, the antagonist can be placed in this category

until it has been shown by experiment to belong elsewhere. It is well known that sulphonamides are more effective bacteriostatic agents the more unfavourable the cellular environment. It is often necessary to make careful quantitative experiments before it is possible to demonstrate that an apparently specific antagonism is due to non-specific growth stimulation. Johnson, Eyring and Kearns (1943), using luminescent bacteria, studied the effect of various media on sulphonamide inhibition of luminescence and concluded that peptone and glucose and possibly arginine, hypoxanthine and serum acted by stimulating luminescence rather than by antagonising sulphonamide. Green and Bielschowsky (1942), in their study of the sulphonamide-antagonistic "p" factor, concluded that it contained, in addition to the specific antagonist P.A.B.A., an unknown non-specific growth stimulant. The apparent sulphonamide antagonism shown by nicotinamide, nicotinic acid or cozymase for *Staph. aureus* may have been due to a non-specific growth stimulatory effect; in cultures of *Escherichia coli* where these substances failed to stimulate growth, they also failed to influence the bacteriostatic action of sulphonamides (Wood and Austrian, 1942). Peptone and yeast extracts exercised some antagonistic effect by growth stimulation of *E. coli* (Rantz and Kirby, 1944). Even physical factors such as temperature may alter significantly the degree of sulphonamide inhibition (Johnson, Eyring and Kearns, 1943).

3 The third type of antagonism which we have listed, combination of antagonist with drug, may occasionally be obvious from inspection of the chemical nature of drug and antagonist, but more subtle grades of combination antagonism also exist. Kimmig and Weselmann (1941) showed by cathoretic methods that all sulphonamides were adsorbed by serum albumin but not by serum globulin. Davis confirmed that proteins cor partially prevent their dial es. In normal human plasma extent of 20 per cent., sulphapyridine 40 per cent., sulphadiazine 55 per cent. and sulphathiazole 75 per cent.; however, the

free p-amino group is not essential for protein binding although it is known to be essential for bacteriostatic action (Davis and Wood, 1942 ; Davis, 1942, 1943).

Urethane and the related barbiturate nembutal exert a marked sulphonamide antagonism which is difficult to account for on any structural analogue basis. The action is not competitive and is only functional at low concentration (McIlwain, 1942a). Johnson and his colleagues have made a quantitative study of the urethane antagonism of sulphonamide inhibition of luminescence in luminescent bacteria, and concluded that, in this system, urethane formed with sulphanilamide an inactive complex (Johnson, Eyring and Kearns, 1943).

7 The fourth important group of sulphonamide antagonists other than P.A.B.A. includes amino acids, thymine and purines. Methionine $\text{CH}_3 \cdot \text{S} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$ was recognised as a sulphonamide antagonist by Harris and Kohn (1941), also by Bliss and Long (1941). Besides being an essential amino acid for higher animals, methionine is an essential constituent of media for certain strains of diphtheria bacillus (Mueller, 1935), for some streptococci (Smiley, Niven and Sherman, 1943), for *Clostridium sporogenes* (Fildes and Richardson, 1935) and for some strains of lactic acid bacteria (Dunn *et al.*, 1947). It does not seem to act as a sulphonamide antagonist by virtue of its growth-promoting properties ; other amino acids such as cystine or tyrosine, which on the same media have greater growth-stimulating effect, have no sulphonamide-antagonistic properties. Reversal of sulphanilamide bacteriostasis by methionine can only be achieved at low concentration of sulphanilamide, so that methionine cannot be a competitive antagonist displacing sulphanilamide from its site of action. Other amino acids, such as glycine, *d.l.*-serine and *d.l.*-allothreonine, do not antagonise sulphanilamide bacteriostasis by themselves, but each enhances the antagonistic action of methionine. Guanine and xanthine also enhance the methionine antagonism of sulphanilamide, but, in the absence of methionine, both are without antagonistic action and indeed enhance sulphonamide bacteriostasis.

There would appear to be some unknown relationship between P.A.B.A., methionine and purino metabolism.

Attempts to elucidate the metabolic function of methionine in *E. coli* have not given much information. It is not oxidised, decarboxylated, deaminated or hydrolysed by washed suspensions of the organism, and cannot replace ammonium ion in the basal medium. It only becomes a growth factor when the organism is repeatedly subcultured in a medium containing sulphanilamide and methionine (Kohn and Harris, 1942). These observations are difficult to interpret, particularly as results with other species of organism under other experimental conditions do not always agree. Much of the hesitation in accepting the simple and straightforward suggestion of Woods as to the relationship between P.A.B.A. and sulphonamides, can probably be ascribed to confusion introduced in attempts to explain these observations.

Kohn (1943) has suggested that his observations can be explained by an extension of Woods' theory. When sulphonamides interfere with P.A.B.A. metabolism, they are said to prevent formation of metabolites whose synthesis is subsequent to, and dependent upon, proper functioning of the P.A.B.A. system. He visualises the process in the case of *Escherichia coli* according to the following scheme (Fig. 21) :—

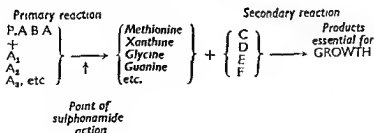


FIG. 21.—Mode of action of sulphonamides (Kohn, 1943).

The primary reactions in which P.A.B.A. takes part, together with various substances of unknown nature, can be inhibited by sulphonamides, some reactions being more sensitive than others. The cell is regarded as dependent upon the proper functioning of these reactions for its supply of secondary metabolites such as methionine. These in turn are

supposed to be necessary for secondary reactions involving formation of still further metabolites, in the absence of which growth is not possible. If only one of the primary reactions is inhibited, say that responsible for methionine supply, then growth can be restored by supplementing the nutrient medium with methionine.

These views have gained support from various observations. With *Escherichia coli*, sulphonamido bacteriostasis is directed against growth rather than against respiration. Ethionine, $C_2H_5.S.CH_2.CH_2.CH(NH_2).COOH$, the higher homologue of methionine, inhibits growth of *E. coli* on a synthetic medium; its effect is completely reversed by one-tenth of its concentration of methionine (Harris and Kohn, 1941). Methoxinine, $CH_3.O.CH_2.CH_2.CH(NH_2).COOH$, the oxygen analogue of methionine, was also growth inhibitory for *E. coli*, the growth-inhibitory effect being prevented by *l*-methionine but not by the *d*-isomer (Roblin, Lampen, English, Cole and Vaughan, 1945). Purines in high concentration were able to replace P.A.B.A. in the nutrition of *Clostridium acetobutylicum* (Housewright and Koser, 1944); with *Acetobacter suboxydans*, which also requires P.A.B.A. as a growth factor, addition of purines to the growth medium increased growth at low P.A.B.A. concentrations, but not at high concentrations (Landy and Streightoff, 1943).

Strong support of Kohn's theory also comes from a study of the nutritive requirements of a strain of *Escherichia coli* produced by exposure of a normal strain to X-rays. The variant strain required P.A.B.A. as a growth factor, but growth response to P.A.B.A. was enhanced by the presence of amino acids, of which the most important was methionine. In the absence of amino acids, purines delayed growth, but in their presence purines promoted growth. In the presence of both amino acids and purines, the P.A.B.A. requirements fell from 0.0012% per c.c. to 0.00011% per c.c. Thymine was practically inactive alone, but in the presence of purines it supported slow growth. A medium containing thymine, purines and amino acids enabled the organism to dispense altogether with P.A.B.A. In this medium both the parent

strain and the variant were highly resistant to sulphonamides (Lampen, Roepke and Jones, 1946).

The amount of sulphanilamide required for maximum growth inhibition of *Lactobacillus arabinosus* in the presence of adenine or other purines was ten times that required in the absence of purines (Shive and Roberts, 1946). Methionine was without effect as a sulphanilamide antagonist for this organism, either in the presence or absence of purines. With *Escherichia coli*, on the other hand, methionine by itself showed some antagonism, while purines had no effect; a mixture of methionine and xanthine or guanine raised the sulphonamide concentration necessary for inhibition by a factor of ten. The P.A.B.A. analogue, 4-amino-2-chlorobenzoic acid, acted as a growth inhibitor antagonised competitively by P.A.B.A., but was inactive in the presence of methionine.

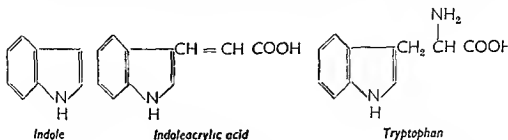
These results all suggest that P.A.B.A. is part of a cellular mechanism for the synthesis of purines, certain amino acids and possibly pyrimidines, and that the synthesis of these essential metabolites is prevented by sulphonamides.

Essential metabolites as non-competitive drug antagonists

The antagonism of sulphonamides by the combined action of amino acids, purines and pyrimidines is non-competitive, and probably takes place through replacement of an intracellular source of metabolite by an extracellular supply. Other examples of non-competitive reversal of growth inhibition which have been recognised can also be explained on this basis.

Fildes (1941, 1945) showed that tryptophan is an essential metabolite for many bacteria, some of which are capable of synthesising their requirements from indole. Indoleacrylic acid is an effective inhibitor of growth in an indole medium, but the inhibition can be completely reversed by addition to the medium of a small quantity of tryptophan. The relationship is non-competitive since the same amount of tryptophan is required to restore growth irrespective of the concentration of indoleacrylic acid, a fivefold increase in indoleacrylic acid necessitating no further increase in tryptophan. Indoleacrylic acid was shown to prevent the synthesis of tryptophan which

probably occurs by condensation of indole with serine. Addition of preformed tryptophan to the medium allows an essential enzymic process related to growth to proceed, despite



the inability of the organism to synthesise tryptophan. Various antagonists and tryptophan inhibit here again the effect is tryptophan. Indole itself antagonises in a competitive manner (Fildes and Rydon, 1947).

This example differs somewhat from the sulphonamide methionine relationship where antagonism is competitive over a small range and incomplete at higher sulphonamide concentrations. It is closely analogous to the effect observed by Lampen (p. 205) with an "aminobenzoic-less" mutant of *Escherichia coli* whose growth in absence of P.A.B.A. was completely restored by a mixture of thymine, purines and amino acids and was then no longer susceptible to inhibition by sulphonamides.

A further example of non-competitive antagonism reported by Beerstecher and Shive (1947 *a* and *b*) seems to have a similar basis. Tyrosine had no effect on the bacteriostatic action of β -hydroxyphenylalanine which inhibited *Escherichia coli* by competition with phenylalanine, it did reverse the bacteriostatic action of thienylalanine, which also competed with phenylalanine. Apparently, phenylalanine is necessary for at least two different types of reaction in *E. coli*; one of these is inhibited by β -hydroxyphenylalanine and produces unknown products; the other is inhibited by thienylalanine and is normally required by the cell for synthesis of tyrosine. If free tyrosine is supplied in the medium, the organism no longer requires an enzyme system for synthesis of tyrosine,

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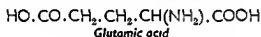
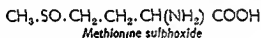
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Presumably imidazolidonecaproic acid competes with desthiobiotin and prevents its conversion to biotin. Such an interpretation is confirmed by the fact that biotin also antagonises imidazolidonecaproic acid, but in a non-competitive manner (Rogers and Shive, 1947; Dittmer and du Vigneaud, 1947).

Methionine sulphoxide has been investigated as a growth-inhibitory analogue of glutamic acid. The sulphoxide apparently prevents amidation of glutamic acid to glutamine since it is antagonised non-competitively by glutamine (Waelsch, Owades, Miller and Borek, 1946). Support for this view is provided by the report of Elliott and Gale (1948) that the enzyme system of *Staph. aureus* which converts glutamic acid to glutamine is inhibited by methionine sulphoxide, inhibition being competitive with respect to glutamic acid.



Folic acid and the site of sulphonamide inhibition

The above examples make it apparent that antagonism of a bacteriostatic substance may be achieved either by adding a metabolite which can compete with the drug at a reactive centre, or alternatively by supplying the product which cannot be synthesised in the presence of drug. In the first case only, the relationship will have the characteristics of competitive inhibition.

If these principles are borne in mind, recent studies of the relationship of pteroylglutamic acid (folic acid) to sulphonamide inhibition indicate one site of action of sulphonamides (Lampen and Jones, 1946 *a* and *b*). We have already noted (Chapter III) that growth of some organisms in the presence of P.A.B.A. is accompanied by folic acid synthesis. Miller (1944) noted that, when bacteria were grown in sub-inhibitory concentrations of sulphonamide, the amount of folic acid synthesised was markedly reduced. Disclosure of the chemical

and is accordingly no longer susceptible to inhibition by thienylalanine (Fig. 22). It should be noted that this scheme is based on the assumption that phenylalanine is a precursor of tyrosine for *E. coli*; this does not agree with work of Simmonds, Tatum and Fruton (1947) on two mutant strains of *E. coli*. These workers suggest that the mutants do not synthesise tyrosine from phenylalanine.

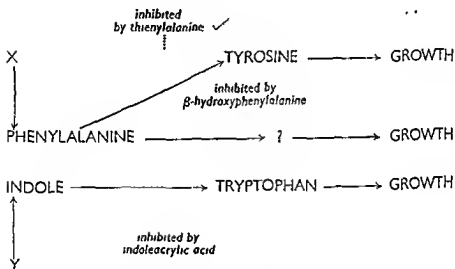
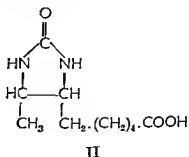
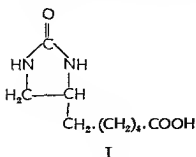


FIG. 22.—Non-competitive antagonism in amino acid utilisation.

Another example of antagonism by two closely-related metabolites, one a competitive and the other a non-competitive antagonist, may be cited from the field of biotin chemistry (cf. p. 142). Imidazolidonecaproic acid (I) is growth-inhibitory for several micro-organisms, and is antagonised competitively by the biotin precursor desthiobiotin (II).



bacteriostatic action of sulphonamides in several organisms, it cannot replace P.A.B.A. as a growth factor for *Lactobacillus arabinosus* (Sarett, 1947) or for the "aminobenzoic acid-less"

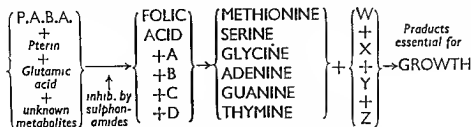
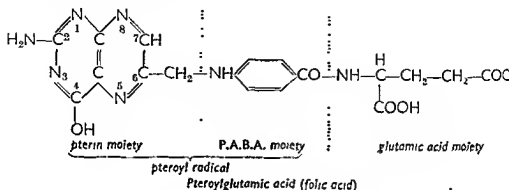


FIG. 23.—Mode of action of sulphonamides.

mutant of *Escherichia coli* studied by Lampen, Roepke and Jones (1946). This probably means that P.A.B.A. has several functions besides pteroylglutamic acid synthesis (*cf.* Chapter III).

Detailed study of pteroylglutamic acid analogues as growth inhibitors has provided confirmatory evidence for the mode of action of sulphonamides. 7-Methylfolio acid, the homologue of pteroylglutamic acid with an additional methyl group at position 7 in the pterin ring, acts as a folio acid displacing agent (Martin, Tolman and Moss, 1947 *a* and *b*). With *Staph. aureus*, the growth-inhibitory action of 7-methylfolio acid was counteracted by P.A.B.A., by pteroylglutamic acid and by pterioic acid or even by sulphathiazole, but not by glutamic acid or by *p*-aminobenzoylglutamic acid. The inhibitory action of sulphathiazole against this strain of staphylococcus was antagonised by P.A.B.A., or by pterioic acid but not by pteroylglutamic acid. This last observation is unexpected. Martin, Tolman and Moss (1947*b*) suggest that pterioic acid and not pteroylglutamic acid is involved in staphylococcus metabolism; this conclusion requires further support before it can be considered as established. A group of synthetic 2:4-diaminopteridines has also been tested for growth-inhibitory action and as pteroylglutamic acid displacing agents against several micro-organisms; some possessed antibacterial activity which was antagonised competitively by pteroylglutamic acid (Daniel, Norris, Scott and Heuser, 1947; Daniel and Norris, 1947). We have already seen that sulphathiazolo

structure of folic acid as pteroylglutamic acid (formula below) suggested that sulphonamides might displace P.A.B.A. from the enzyme surface on which the pteroylglutamic acid molecule was fitted together.

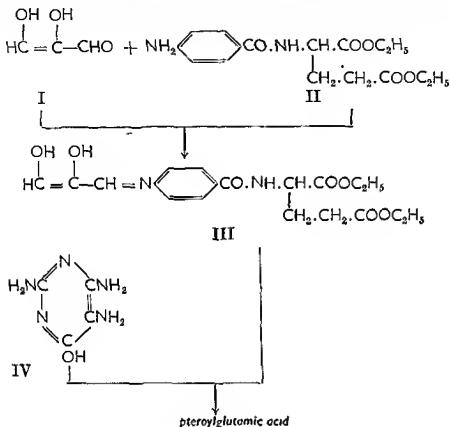


Lampen and Jones found that growth of *Strep. faecalis* and *Lactobacillus casei* in the presence of pteroylglutamic acid was insensitive to sulphonamides. Strains which were able to synthesise pteroylglutamic acid were found to be sensitive to sulphonamides under conditions where they were forced to synthesise this essential metabolite, but insensitive when it was supplied in the medium. A competitive inhibition occurred between sulphadiazine and P.A.B.A. or between sulphadiazine and *p*-aminobenzoylglutamic acid, but the antagonism of sulphadiazine by pteroylglutamic acid was non-competitive. Thymine also antagonised in a non-competitive manner. The same relationship was found with other sulphonamides and indicates that sulphonamides compete, in these organisms, with P.A.B.A. for an enzymic mechanism involved in the conversion of P.A.B.A. to pteroylglutamic acid.

These results, taken in conjunction with the results on amino acid and purine antagonism of sulphonamides, and with the demonstration that amino acids, purines and pyrimidines can replace P.A.B.A. in the growth medium of "P.A.B.A.-exacting" organisms, suggest that Kohn's scheme (Fig. 21) may be very tentatively extended as follows (Fig. 23).

At present the exact relationship between pteroylglutamic acid and amino acid, purine and pyrimidine synthesis is obscure. Although pteroylglutamic acid antagonises the

amides, by suggesting that the primary reason for the effectiveness of sulphonamides in preventing growth of certain pathogenic bacteria resides in the need of those bacteria to synthesise



pteroylglutamic acid or a similar compound. This makes it apparent, also, why sulphonamides do not inhibit effectively all bacteria. An organism which does not carry out this synthesis, but depends instead on its environment for a supply of folic acid, will not be inhibited to the same extent by sulphonamides. It should be kept in mind, however, that any sulphonamide may have several secondary sites of inhibitory action which become obvious in those organisms which do not synthesise folic acid.

Antagonists and sulphonamide therapy

Besides their interest as pointers to the mode of drug action, sulphonamide antagonists are of considerable practical importance, and account for differences observed between the

reduced synthesis of pteroylglutamic acid. Diaminopteridines enhanced sulphonamide bacteriostasis in organisms which normally synthesise pteroylglutamic acid.

Two further links in the chain of evidence relating sulphonamide inhibition with failure to synthesise pterins and purines may be mentioned. It has been known for some time (Fox, 1942; Stetten and Fox, 1945) that an aromatic amine accumulates in the medium when *Escherichia coli* is grown in a synthetic medium containing salts, amino acids, glucose and sulphonamides. In the presence of sufficient P.A.B.A. to block sulphonamide action the amine is not formed. Stetten and Fox suggested that the amine might be an intermediate in some metabolic reaction which was blocked by sulphonamide. The amine has now been identified as 5-amino-4-imidazolecarboxyamide, a possible precursor of purines (Shive *et al.*, 1947), and has been shown to be formed in amounts directly proportional to the glycine content of the medium (Ravel, Eakin and Shive, 1948).

A second line of evidence derives from the suggestion that sulphonamides prevent bacterial growth by displacing P.A.B.A. from combination with glucoreductone (O'Meara, McNally and Nelson, 1947). Forrest and Walker (1948 *a* and *b*) have found that under suitable conditions condensation between triamino-hydroxypyrimidine and glucose gives rise to a pterin with an absorption spectrum essentially the same as that given by the pteroyl radical of pteroylglutamic acid; moreover, glucoreductone (I below) condenses readily with the ester of *p*-aminobenzoylglutamic acid (II) to give III. This condensation product combines readily with 2:4:5-triamino-6-hydroxypyrimidine (IV) to give pteroylglutamic acid (Angier *et al.*, 1948).

Essentially similar results have been obtained independently by Forrest and Walker (unpub.).

These results indicate that Kohn's scheme, Fig. 23, might be still further modified, the term pterin being replaced by triaminohydroxypyrimidine+glucoreductone.

From all these lines of evidence, we may sum up the present state of knowledge regarding the mode of action of sulphon-

amide group produced a bacteriostatic compound stimulated synthesis of other metabolite analogues in which similar structural change was made. Nicotinic acid or nicotinamide is essential for the growth of various micro-organisms and, as already noted, cannot be replaced by other pyridine derivatives not substituted in the 3-position (Chapter III). Pyridine-3-carboxylic acid esters can replace nicotinic acid to some extent, probably because they can be converted biologically to the free acid (Dorfman, Koser, Reames, Swingle and Saunders, 1939). Pyridine-3-sulphonic acid, instead of supporting growth, acts as a growth inhibitor for some organisms and its growth-inhibitory action is reversed by nicotinic acid (McIlwain, 1940).



Nicotinic acid



Pyridine-3-sulphonic acid

The narrow line between growth inhibition and growth promotion must be emphasised here. Organisms which do not require nicotinic acid for growth were not inhibited by the related sulphonic acid; some micro-organisms, such as *Proteus vulgaris*, which were inhibited by pyridine sulphonic acid when nicotinic acid was the growth factor were not inhibited when nicotinic acid was replaced by nicotinamide. Other organisms actually utilised pyridine-3-sulphonic acid as a growth factor (Lwoff and Querido, 1939). With pyridine-3-sulphonic acid amide, a somewhat similar type of action was observed. This compound was bacteriostatic for organisms requiring nicotinamide as a growth factor, but had little effect even at high concentrations on organisms able to synthesise their own nicotinamide requirements. The inhibitory action was antagonised by nicotinamide.

Further extension of the idea of replacing a carboxyl group by a sulphonic acid group followed; pantoyl-taurine, the sulphonic acid analogue of pantothenic acid, was found to be bacteriostatic for those organisms which required pantothenic acid as a growth factor (Snell, 1941; Kuhn, Wieland

in-vivo and *in-vitro* effectiveness of sulphonamides as bacteriostatic agents. Because of the presence of antagonists such as protein, amino acids and P.A.B.A. in body tissues and fluids a sulphonamide which may prevent bacterial growth in culture media may be of no use therapeutically. For example *Clostridium sordelli*, which is strongly inhibited by sulphonamides *in vitro*, cannot be controlled in animal infections (Reed, Orr and Reed, 1944).

Other metabolite analogues

The amount of space devoted to a discussion of competitive inhibition by sulphonamides, besides being a tribute to the importance of sulphonamide drugs, is an illustration of the valuable stimulus provided by study of competitive inhibition to general theories of drug action. In searching for the perfect chemotherapeutic remedy for any disease, such factors as absorption, excretion, toxicity and distribution in the host must be considered, but before systematic improvement becomes possible, variables must be eliminated and the effect of structure on each factor studied separately.

The information provided by the P.A.B.A. antagonism of sulphonamides has turned much chemotherapeutic research from brilliant exploitation of chance observations to purposeful development of growth-inhibitory metabolite analogues. For the present, this new guidance of the trend of research may have the anomalous result that, in relation to the effort expended, fewer clinically useful drugs will be added to the pharmacopœa; but the body of information collected on the way will have greatly widened the perspective and has already begun to provide a biochemical foundation for the study of drug action.

In discussing the metabolic requirements of micro-organisms, we gave a number of examples of the substitution of an essential metabolite by a compound of closely related chemical structure, and noted how growth-promoting activity would fall as the substitute became less suitable for biological conversion to the parent structure. The recognition that substitution of the carboxyl group of P.A.B.A. by a sulphon-

amide group produced a bacteriostatic compound stimulated synthesis of other metabolite analogues in which similar structural change was made. Nicotinic acid or nicotinamide is essential for the growth of various micro-organisms and, as already noted, cannot be replaced by other pyridine derivatives not substituted in the 3-position (Chapter III). Pyridine-3-carboxylic acid esters can replace nicotinic acid to some extent, probably because they can be converted biologically to the free acid (Dorfman, Koser, Reames, Swingle and Saunders, 1939). Pyridine-3-sulphonic acid, instead of supporting growth, acts as a growth inhibitor for some organisms and its growth-inhibitory action is reversed by nicotinic acid (McIlwain, 1940).



Nicotinic acid



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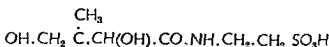
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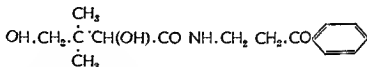
and Moller, 1941; McIlwain, 1942b). The bacteriostatic action was competitively reversed by pantothenic acid.



Pantothenic acid



Pantoyl-taurine



Phenylpantothenone

The close relationship of bacteriostatic action to the metabolic character of the cell is further emphasised by the observation that in the case of organisms which require for growth only one "half" of the pantothenic acid molecule in the medium, a structural analogue of that half may inhibit growth. Thus, β -aminobutyric acid and isoserine inhibited the growth of yeast induced by β -alanine (Nielsen and Johansen, 1943); taurine inhibited growth of *Acetobacter suboxydans* and *Clostridium septicum* more in the presence of the pantoyl moiety than in the presence of intact pantothenate, and the inhibition was reversed by β -alanine (Sarett and Cheldelin, 1945; Ryan, Schneider and Ballentine, 1947).

Pantoyl-taurine has been tried as a chemotherapeutic remedy in animal infections and exerted some protective action against streptococcal infection, but the rapid rate of excretion and the presence in blood of the natural antagonist (pantothenic acid) rendered the compound relatively ineffective (McIlwain and Hawking, 1943). Systematic variation of structure has since led to other analogues with much greater bacteriostatic action (Shive and Snell, 1945; Snell and Shive, 1945; Woolley and Collyer, 1945; Mead, Rapport, Sencar, Maynard and Koepfli, 1946; Snell, 1946). One of these,

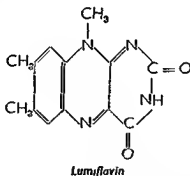
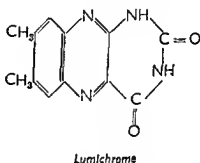
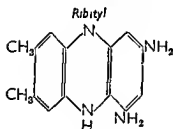
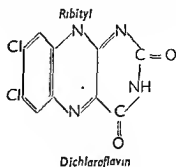
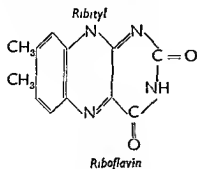
phenylpantothenone (formula above), is particularly interesting, since it inhibits growth of organisms which do not require added pantothenic acid as well as those requiring this metabolite, but its growth-inhibitory effect is reversed by pantothenic acid only in those organisms for which pantothenic acid is a growth factor.

Pantothenic acid analogues have been used with some success in experimental malaria infections (Mead, Rapport, Senear, Maynard and Koepfli, 1946; Brackett, Waletzky and Baker, 1946; Senear, Rapport and Koepfli, 1947). Pantothenic acid is probably a growth factor for the parasite, since sporozoite-induced infections in chicks were slower in developing, and less severe, in birds maintained on a pantothenic acid deficient diet. Most of the drugs which were active, also caused pantothenic acid deficiency in the chick, but some were apparently distributed so that they preferentially inhibited parasite growth. Exoerythrocytic infections were not inhibited in the same way, probably because of the higher concentration of pantothenic acid in tissues than in blood.

As already noted, riboflavin plays an important role as a component of many enzyme systems, and is an essential metabolite for many micro-organisms. Various synthetic analogues were found to possess reduced growth-promoting action (see Chapter III); others, such as dichloroflavin, were growth-inhibitory for those bacteria which cannot synthesise their own supply of riboflavin (Kuhn, Weygand and Möller, 1943). A phenazine analogue, 2:4-diamino-6:7-dimethyl-9-ribityl-9:10-dihydrophenazine has also been found to inhibit growth of *Lactobacillus casei* (Woolley, 1944b); while a "riboflavin-less" mutant of *Neurospora* was inhibited by both lumichrome and lumiflavin (Mitchell and Houlahan, 1946). In all these cases, the inhibition was reversed by addition of riboflavin to the growth medium (Formulæ, p. 218).

We have seen that taurine can antagonise β -alanine in the synthesis of the pantothenic acid molecule. Sulphonic acid analogues of α -amino acids also antagonise the natural amino acids (McIlwain, 1941b). Cysteic acid, the analogue of aspartic acid where the ω -carboxyl group is replaced by

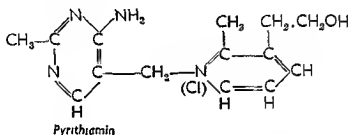
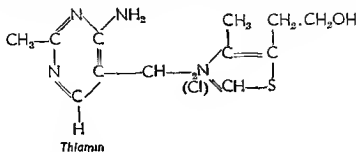
sulphonic acid, is toxic to various micro-organisms and is antagonised competitively by aspartic acid (Ravel and Shive,



1946). In *Escherichia coli*, one reaction prevented by cysteine acid is thought to be decarboxylation of aspartic acid to β -alanine, since toxicity is not apparent in the presence of pantothenic acid or β -alanine.

The relationship between growth requirements and inhibition by a growth-factor analogue has been particularly fully worked out for the thiamin analogue pyriethiamin, in which the thiazole ring of thiamin is replaced by a pyridine ring (Tracy and Elderfield, 1940). Many organisms which

cannot synthesise thiamin, and require the intact thiamin molecule are prevented from growth by low concentrations of pyriethiamin, but organisms which can synthesise the



complete thiamin molecule are highly resistant to growth inhibition (Woolley and White, 1943b; Wyss, 1943). It will be remembered that some micro-organisms can synthesise the complete thiamin molecule if supplied with both the pyrimidine and the thiazole portions; others have greater synthetic powers and can synthesise one half if supplied with the other half. In the case of organisms which require only the pyrimidine half, the growth-inhibitory action of pyriethiamin can be reversed by addition of the pyrimidine to the medium.

Robbins (1941) found that three fungi differed in their response to pyriethiamin in accordance with their differing growth requirements. *Phytophthora cinnamomi*, which requires the intact thiamin molecule, could not grow in the presence of low concentrations of pyriethiamin; *Phycomyces blakesleeana*, which could grow on a mixture of thiazole and pyrimidine, was able to split pyriethiamin and use the pyrimidine half if supplied with the thiazole half; *Pythiomyces gonapodioides*, which can synthesise the thiazole half, was able to grow on pyriethiamin by using it as a source of pyrimidine. In *Neurospora*, on the other hand, there is no relationship

between capacity for thiamin synthesis and ease of inhibition by pyrithiamin (Tatum and Bell, 1946).

Pyrithiamin cannot be used as a chemotherapeutic drug, since at blood concentrations which are non-toxic to experimental animals, the drug is not bacteriostatic (Wyss, 1943). As in the case of pantothenic acid analogues, this difficulty is related to the fact that many bacterial growth factors are also essential nutrients for higher animals. During evolution, much of the enzymic make-up of life has remained essentially unchanged, and the same substances are necessary throughout the non-photosynthetic living world for the elaboration of new enzymes and for their catalytic functions.

In an individually-variable population of micro-organisms, it is by no means easy to analyse the biochemical effect of metabolite analogues except in terms of a growth effect. In higher animals, the physiological and histological effects induced by vitamin (essential metabolite) deficiencies have been more fully characterised, and the effect of feeding a growth-inhibitory metabolite analogue has been analysed, not only in terms of growth inhibition, but also in terms of the pathological changes induced.

When pyrithiamin is fed to mice, symptoms characteristic of thiamin (vitamin B₁) deficiency are displayed and the condition can be cured by the feeding of a sufficient excess of thiamin (Woolley and White, 1943a). Isoriboflavin, the 5:6-dimethyl analogue of riboflavin, when fed to rats, prevents growth and gives rise to symptoms characteristic of riboflavin deficiency (Emerson and Tishler, 1944); the pbenazine analogue of riboflavin produces similar vitamin deficiency symptoms in mice (Woolley, 1944b); both these effects are reversed by feeding riboflavin. Mice do not normally require nicotinic acid in their diet, but feeding of 3-acetyl pyridine produced the symptoms known to occur in other animals fed on a nicotinic acid free diet (Woolley, 1945); the symptoms disappeared rapidly when nicotinic acid was added to the diet. A condition resembling scurvy can be induced by feeding glucoascorbic acid and the condition can be cleared up by addition of excess ascorbic acid to the diet

(Woolley, 1944*d*; Woolley and Krampitz, 1943). Symptoms of vitamin K deficiency, namely a large increase in the coagulation time of the blood, may be induced in the rat, an animal not normally affected by lack of this vitamin, by feeding dicumarol (Overman, Field, Baumann and Link, 1942). The condition does not develop when large quantities of vitamin K are fed along with dicumarol. The pantothenic acid analogues tested against malarial infections in chicks (p. 217) caused symptoms of pantothenic acid deficiency which were relieved by feeding pantothenate (Brackett, Waletzky and Baker, 1946).

With these few examples before us it is convenient to pause and take stock of the position. As already emphasised, competitive inhibition in isolated enzyme systems has been found to occur when a compound structurally similar to a natural substrate competes with that substrate for an active group on an enzyme surface. The characteristics of competitive inhibition in enzyme systems were defined as follows :—

- (1) At a fixed concentration of inhibitor the degree of inhibition is inversely proportional to substrate concentration ;
- (2) for a given degree of inhibition the ratio of substrate concentration to inhibitor concentration is constant over a wide concentration range ;
- (3) with a series of structurally related inhibitors acting on the same enzyme, inhibitions are proportional to the dissociation constants of the enzyme-inhibitor complexes.

It has been possible to apply these criteria to growth inhibition by metabolite analogues, and to reversal of growth inhibition by the related essential metabolites. The metabolite-inhibitor relationship is usually consistent with the assumption that the two compounds are in competition for a common site on some cellular enzyme. In other words, the metabolite analogue appears to prevent or reduce cellular utilisation of essential metabolite (*cf.* Mellwain and Hughes, 1945; Mellwain, 1945; Sarett, 1946). Where non-competitive antagonism exists, the

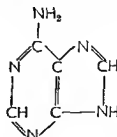
analogue may inhibit synthesis of the metabolite, as in the case of folic acid or tryptophan.

In the majority of cases so far examined, a metabolite analogue is only effective as a growth inhibitor for those strains of micro-organism which require an external source of the related essential metabolite; thus, pyriethiamin inhibits at low concentrations only those organisms which require an external source of the intact thiamin molecule. It is less effective against organisms which can synthesise one half of the molecule, and practically ineffective against organisms which require neither the pyrimidine nor the thiazole "half." In a similar fashion, pantooyl-taurine only inhibits growth of organisms which normally require added pantothenic acid for growth; pyridine-3-sulphonic acid only inhibits growth of strains which are unable to synthesise nicotinic acid. Desthio-biotin acts as a growth inhibitor for *Lactobacillus casei*, an organism which requires preformed biotin. In other less-exacting organisms, the same compound acts as a growth factor and a precursor of biotin (Lilly and Leonian, 1944; Dittmer, Melville and du Vigneaud, 1944) (see p. 141).

In contrast to the above group, the sulphonamides inhibit organisms which normally synthesise their own requirements of P.A.B.A., as well as those which require P.A.B.A. as a constituent of the medium. Sulphonamides inhibit conversion of both endogenous and exogenous P.A.B.A. into pteroylglutamic acid and so prevent growth of organisms which



Benzimidazole



Adenine

synthesise their own supplies of pteroylglutamic acid. Benzimidazole inhibits growth of organisms which do not require added adenine (Woolley, 1944a), and phenylpantothenone is

growth-inhibitory for organisms able to synthesise pantothenate. In the case of sulphonamides and benzimidazole, excess of the natural metabolite added to the medium reverses the growth-inhibitory effect of the analogue in a competitive manner. The question naturally arises—Why do sulphanilamide and benzimidazole inhibit growth irrespective of the growth requirements of the strain, although they are susceptible to antagonism by excess of the related essential metabolite? Other metabolite analogues only inhibit organisms for which the metabolite is a growth factor.

It is impossible, as yet, to give a clear-cut answer to this question. If we visualise the possible explanations we may perhaps help to suggest an experimental approach which can provide an answer to the problem, and incidentally provide a guide to the synthesis of chemotherapeutically-effective metabolite analogues other than the sulphonamides.

A number of cases have been reported where biochemical mutation induced by exposure of a wild strain of the mould *Neurospora* to X-rays results in failure to synthesise a metabolite which is readily synthesised by the wild strain (see p. 108). The synthetic deficiency is often accompanied by a specific sensitivity to inhibition by metabolite analogues, which is lacking in other mutant strains and in the parent strain. The most striking case is the specific inhibition of a "lysine-less" mutant by arginine; arginine does not inhibit wild-type *Neurospora*, and therefore does not block utilisation of endogenous lysine (Doermann, 1944). The different effect in the two cases can best be explained by the legitimate assumption that, in the wild type, arginine passes from the medium through the cell wall to reach the cellular metabolic system and is immediately metabolised; it never reaches the site of utilisation of endogenously-synthesised lysine. In the mutant "lysine-less" strain, both arginine and lysine pass the cell wall together, and both have to be acted on by specific enzymes in the presence of one another. The close structural similarity between the two amino acids enables either to displace the other from its specific enzyme in a competitive manner, so that excess of arginine results in a failure of the cellular

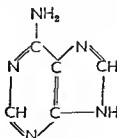
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Adenine

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preformed pantothenic acid may be due to its rapid hydrolysis within the cell, since indirect evidence has been obtained for the occurrence of a small amount of hydrolysis in the medium in contact with bacteria (Stansly and Alverson, 1946). This might also account for the fact that pantooyl-aurine was found to be a growth factor for a pantoic acid exacting strain of *Clostridium septicum* (Ryan, Schneider and Ballentine, 1947).

Another explanation of the failure of anti-metabolites to inhibit growth of organisms which synthesise their own requirements of related metabolite must also be considered. As we have seen, the growth-inhibitory action of a metabolite analogue is effectively antagonised by a sufficient concentration of the metabolite. Obviously, if a cell synthesises its own supply of metabolite, the concentration of that metabolite within the cell wall may be such that any metabolite analogue passing into the cell is effectively antagonised. Examples have already been quoted of the association of increased P.A.B.A. synthesis with increased resistance to sulphonamides. As will be indicated in the discussion of drug resistance (Chapter VI), all cases of increased resistance cannot be explained in terms of increased production of antagonist, so that each drug and each species of micro-organism must be regarded as a separate problem. One case has been examined in some detail (Woolley and White, 1943*b*). The amount of thiamin synthesised by those organisms for which it is not a growth factor was measured quantitatively; although apparently quite adequate for growth in absence of pyriethiamin, it was obviously insufficient to antagonise the quantities of pyriethiamin used in the inhibition tests.

In this brief outline of competitive metabolite antagonists it has not been possible to detail the numerous examples scattered throughout the chemical, biochemical and medical literature, or to deal with the recent successful clinical development of histamine antagonists. More detailed accounts of the whole subject by Roblin (1946) and Woolley (1947) are available.

metabolic system to take up sufficient lysine for protein synthesis.

This view of the course of events is supported by the results of McIlwain (1945) on the inhibition of pantothenate utilisation by pantoyl-taurine, and by those of Sarett (1946) on the inhibition of riboflavin utilisation by riboflavin analogues. In both cases, the metabolite analogue appeared to block utilisation of the metabolite by passing through the cell wall with the metabolite and arriving at the same time at the initial reaction site which is responsible for the uptake of the metabolite.

Presumably, metabolite analogues may fail to inhibit growth of organisms which synthesise their own supply of metabolite because, as in the case of arginine, the analogues are caught up in the metabolic system designed for the natural metabolite as soon as they pass the cell wall, and then are rapidly metabolised to a form which cannot interfere with the secondary utilisation of endogenously-synthesised metabolite. If this assumption is correct, there should be traceable a difference between the metabolic fate of anti-metabolites which are only effective growth inhibitors for organisms which require preformed metabolites (*e.g.* pyriithiamin), and anti-metabolites which inhibit growth of non-exacting as well as related exacting strains. In other words, an effective growth inhibitor would have to possess considerable biological stability such that it could not be readily converted by metabolic enzymes to an inactive form; presumably sulphanilamide, phenylpantothenone and benzimidazole fall into this category.

An artificially produced pyriithiamin-fast strain of yeast was found to have developed a metabolic system for the cleavage of pyriithiamin into its component parts; the system was also found in those organisms which normally synthesised their own requirements of thiamin (Woolley, 1944c). It seems probable therefore, that in the thiamin synthesisers the inhibitory analogue is metabolised to a harmless form, long before it reaches the vital site in the cell at which thiamin is synthesised and utilised intracellularly. The failure of pantoyl-taurine to inhibit organisms not requiring

In seeking reactions specific to parasite and absent from host, that group of enzymes and coenzymes concerned primarily with energy-yielding oxidative reactions (about which we know most) does not look promising, since micro-organisms and higher animals metabolise the same foodstuffs by closely similar pathways. Proteins are, however, species-specific and therefore some species-specific synthetic processes must go on during growth to build up their patterns. A logical point of attack would then seem to be the mechanisms concerned with protein synthesis. Surprisingly little evidence is available to show whether the recognised amino acids are all common to animal and bacterium, and a systematic investigation of protein from micro-organisms seems highly desirable. To upset protein synthesis, the organism might be presented with amino acid analogues capable of being built up in peptide linkage but incapable of proper function in the completed protein. Alternatively, peptides might be synthesised capable of inhibiting by their unnatural configuration the build-up or breakdown essential for vital function. The recognition of gramicidin as a peptide and of penicillin and streptomycin as closely related to amino acids is suggestive of further profitable exploration in this field (Work, 1948).

Provided we know enough about the building blocks used by micro-organisms, we may be able to imitate these sufficiently closely for the analogue to be caught up in a synthetic process for which it is unsuited. Before a metabolite analogue can play such a part, it must, however, be sufficiently stable to resist breakdown during metabolism and it must also resemble a natural metabolite so closely that an enzyme, a highly selective and specific catalyst, must be unable to reject it in preference to its natural substrate.

The chemotherapy of virus infections is still very much in the embryonic phase. Little is known of the biochemical activities of viruses. A possible line of chemotherapeutic attack has been suggested by a study of the nature of combination between virus and host. In the case of certain bacterial viruses which infect *Escherichia coli*, tryptophan is a necessary co-factor for adsorption of virus on the host cell

Possibilities and limitations of metabolite analogues

As we have pointed out already, many metabolite analogues cannot be used chemotherapeutically because they produce specific vitamin deficiency diseases in the host animal. Such a difficulty is inevitable in the design of new chemotherapeutic drugs, since these are often structural analogues of metabolites essential to host as well as to parasite. However, the success achieved in rendering less toxic the arsenoxides and pentavalent organic arsenicals and antimonials, should encourage development of new metabolite analogues, even when first attempts have led to drugs which are equally toxic to parasite and host. The selective parasitocidal action of organo-metallic drugs must depend very largely upon selective distribution, which favours concentration of the drug in parasite rather than host cells. Some success has been achieved in lowering toxicity, for the host, of pantothenate analogues, without impairment of their antimalarial activity (Brackett, Waletzky and Baker, 1946).

The ideal approach to chemotherapy would be through obstruction of an enzyme system or metabolite essential to parasite but non-existent in or less essential to host. Among the sulphonamides we have stumbled accidentally against one such group. Following upon the recognition of folic acid (pteroylglutamic acid) as a derivative of P.A.B.A., and the demonstration that sulphonamides prevent synthesis of pteroylglutamic acid, it is apparent that only cells which are obliged to synthesise pteroylglutamic acid will be highly susceptible to sulphonamides. Cells which draw preformed pteroylglutamic acid from their medium will be more resistant. Various Gram-negative bacteria and animal cells belong to the latter category. If dosage of sulphonamide is too high or too prolonged, those cells of the host which require to multiply rapidly (the cells of the bone marrow), may show signs of inhibition of cell division, possibly because their supply of folic acid is slowly exhausted. Granulocytopenia induced by sulphonamides is rapidly cured by administration of folic acid (Daft and Sebrell, 1945).

to a quite different mechanism. Mapharsen, an effective trypanocide, is also toxic to *E. coli*, but in this case the effect is not reversed by P.A.B.A. ; thus, we apparently have two possible modes of action of organic arsenicals on *E. coli*. Knowing these facts, we can conclude that modifications in structure which lead to enhanced trypanocidal activity among arsenoxides are unlikely to be profitable in increasing bacteriostasis of *E. coli* by sulphonamides or even by atoxyl. Trypanocidal arsenoxides in general are antagonised in their trypanocidal action by glutathione or cysteine, but not by P.A.B.A. An exception to this was found in γ -(*p*-arsenophenyl)-butyric acid which was antagonised by both compounds (Williamson and Lourie, 1946). The only explanation for this action is to assume that the drug acts ultimately in the same manner as other trypanocidal arsenicals, but that P.A.B.A. may be preventing or limiting admission into the trypanosome cell (see also p. 296).

Similar studies have shown that the antimalarial activity of certain sulphonamides is not related to their similarity to P.A.B.A. The antimalarial activity of 2-metanilamido-5-chloropyrimidine and related metanilamides was not antagonised by P.A.B.A. The sulphadiazine analogue with a 5-halogen in the pyrimidino ring (2-sulphanilamido-5-bromopyrimidine) was bacteriostatic for *Escherichia coli* and this action was completely antagonised by P.A.B.A. The same compound was also active against malaria (*Plasmodium gallinaceum*), but this action was only partially antagonised by P.A.B.A. (Brackett and Waletzky, 1946 ; English, Clark, Clapp, Seeger and Ebel, 1946).

Non-specific competitive antagonism

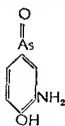
When two related dyes, one of which is an enzyme inhibitor, are added simultaneously to an enzyme preparation, the degree of inhibition observed may be less than when the inhibitory dye is added alone. The harmless dye is in this case competing with the inhibitory dye for the same point on the enzyme surface and so reducing competitively the degree of inhibition. Numerous examples of this effect are

(Anderson, 1945). 5-Methyltryptophan appeared to have an action somewhat similar to tryptophan in that it permitted adsorption of virus on host, but in the presence of this tryptophan analogue the infected cell was not a suitable milieu for virus multiplication (Cohen and Anderson, 1946).

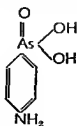
Available evidence suggests that the influenza virus, when it causes hæmagglutination, may react with a carbohydrate group in red cells. Green and Woolley (1947) tested other carbohydrates for their ability to inhibit the reaction by competition with the red cell carbohydrate for carbohydrate-receptor groups on the virus. A number of polysaccharides, particularly apple pectin, were found to be capable of inhibiting hæmagglutination; apple pectin also inhibited growth of the virus in chicken embryo. As the authors themselves point out—"Although the working hypothesis just outlined has led directly to positive experimental results, it does not necessarily mean that this hypothesis is the correct one."

Antagonism and the mode of action of related drugs

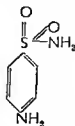
The study of competitive inhibition has provided a useful indication whether two related drugs which are toxic to the same organism are acting at the same key point. Peters (1943) found that both atoxyl and sulphanilamide inhibited growth of *Escherichia coli* on a synthetic medium. In both cases the effect was fully reversed by P.A.B.A. However, sulphanilamide had no trypanocidal effect, while the trypanocidal effect of atoxyl was reversed, not by P.A.B.A., but by cysteine. It is



Mopharsen



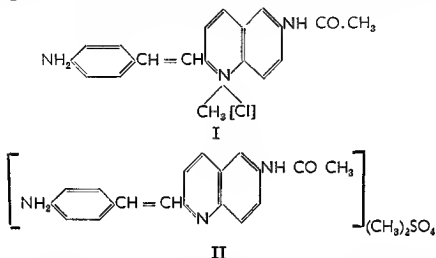
Atoxyl



Sulphanilamide

evident that while atoxyl and sulphanilamide act in the same way on *E. coli*, the toxic effect of atoxyl on trypanosomes is due

(Browning, Cohen, Ellingworth and Gulhransen, 1926, 1929; Browning, Cohen, Cooper and Gulhransen, 1932). An attempt to prepare 2-(*p*-aminostyryl)-6-acetylaminquinoline methochloride by two different methods resulted in two related compounds, one a quaternary salt (I), the other an addition compound of methyl sulphate and base (II). Compound I



was an effective trypanocide in mice infected with *Trypanosoma brucei*; compound II had no trypanocidal action, but was found to antagonise the action of compound I when present in one-tenth the concentration of I. Evidently compound II, although inactive therapeutically, resembled I sufficiently closely to be absorbed in the same way.

Probably the same type of effect is involved in the reversal of atehrin, quinine and propamidine bacteriostases by spermine, spermidine and other polyamines (Snell, 1944a; Silverman and Evans, 1944). The difficulty involved in the interpretation of observed results is well illustrated by this case. *Pseudomonas pyocyanea* was known to oxidise polyamines, including spermidine, and it was reasonable to suppose that inhibition of growth by bacteriostatic bases was due to inhibition of metabolism of the essential growth factor, spermidine. Such a mechanism would necessitate classifying the effect as specific competitive inhibition. Other facts, however, indicate that a non-specific mechanism is involved. In *Escherichia coli*, spermidine was not oxidised or required as a growth factor,

recorded in the literature of enzymology. The only difference between this type of competition and that which we have already discussed lies in the nature of the antagonist. In specific competitive inhibition, the antagonist is a natural substrate (metabolite) or coenzyme; in non-specific competitive inhibition, neither inhibitor nor antagonist is related chemically to the substrate or coenzyme.

The effect of pH on the degree of inhibition of enzymes by basic dyes can be attributed to competition between the hydrogen ions and basic dye ions for certain acidic groups on the enzyme surface. Hydroxyl ions may similarly compete with, and reduce inhibition caused by, toxic anions; such cases are discussed more fully in Chapter VII. Two basic or two acidic drugs may also compete with one another.

There are numerous instances of analogous effects in the field of chemotherapy. Browning and Gulbrandsen (1922) reported that the trypanocidal action of trypaflavine was reduced by parafuchsin when mice, infected with a parafuchsin-resistant strain of trypanosome, were fed with parafuchsin and the infection treated with trypaflavine. Browning suggested the term "*therapeutic interference*" for this type of effect. Similar results were obtained with normal trypanosomes; the action of a variety of trypanocidal drugs, both arsenicals and acridines, was antagonised by parafuchsin and other dyes (Schnitzer, 1926; Schnitzer and Rosenberg, 1926 *a* and *b*; Schnitzer and Silberstein, 1926 *a* and *b*). Hasskó (1935) showed that the protective dye lessened the degree of absorption of acriflavine by trypanosomes.

Interference phenomena can also be demonstrated *in vitro*. Carbon dioxide production from glucose by yeast was inhibited by acriflavine or methyl violet. Methyl violet alone, in sufficiently low concentrations, had no effect, but it caused considerable reduction of the inhibitory effect of acriflavine. Preliminary staining with low concentrations of acriflavine could similarly reduce the toxic effect of high concentrations of methyl violet (Wright and Hirschfelder, 1930).

An interesting case of non-specific competitive inhibition arose from the synthesis of trypanocidal styrylquinolines

The effect of *pH* change on the activity of widely differing types of acidic and basic drugs is in agreement with the ion exchange interpretation. Hydrogen ions antagonise competitively acridine, propamidine, atebtrin, streptothricin and cationic detergents. Elson (1945) gives a diagram, typical of the type of effect observed, for the effect of *pH* change on the antibacterial activity of propamidine (Fig. 24). (For full discussion of effect of *pH* on drug action see Chapter VII).

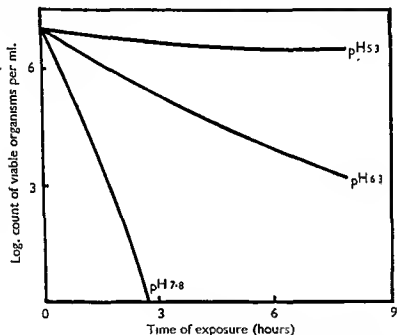


FIG. 24.—Effect of *pH* on the bactericidal action of propamidine. (Elson, 1945.)

It is apparent that no clear-cut line can be drawn between specific and non-specific competitive inhibition, but it is very necessary, when elaborating chemotherapeutic theories based upon nutritional requirements of micro-organisms, to remember that every drug antagonist is not automatically an essential metabolite.

Antagonism of drugs containing arsenic, mercury and antimony

The organic derivatives of arsenic and antimony, used extensively in the treatment of protozoal and spirochætal infections, are also toxic to bacteria and, indeed, to most

but successfully antagonised the bacteriostatic action of propamidine. Certain soil bacilli, capable of growing in a salt-glucose medium containing ammonium phosphate as sole source of nitrogen, were inhibited by high concentrations of atabrin and the bacteriostasis was antagonised by spermidine. Other related organisms incapable of growing in glucose-salt medium were inhibited by low concentration of atabrin, but the bacteriostasis was not antagonised by spermidine. In Chapter IV (p. 165) we showed that atabrin and quinine inhibit a large number of enzymes, probably because of their basic nature; polyamines might well antagonise them by displacement.

Lecithin, also, is capable of antagonising the antibacterial action of diamidines (Elson, 1944) and has a similar protective effect against cationic and anionic detergents (Baker, Harrison and Miller, 1941b) (see Chapter VII).

It is well known that the bactericidal action of dyes depends greatly upon the *pH* of culture media (Browning, Gulbransen and Kennaway, 1919). Stearn and Stearn (1924, 1929) suggested that dyes exercised their bacteriostatic effect mainly in the ionised condition; thus, the cation of a basic dye was visualised as acting by being adsorbed on an acidic group of a cellular protein. Such a mechanism allows *pH* effects to be explained on the basis of non-specific competitive inhibition. On increase of H ion concentration, some of the dye cation will be displaced from its combination with protein by the harmless H ion, so permitting cellular enzymes to resume their normal functioning. In confirmation of their interpretation, Stearn and Stearn pointed out that, among a series of related dyes, increasing bacteriostatic action was associated with increasing base strength. Much evidence not available to the Stearns in 1925 has since tended to strengthen the belief in their interpretation (see Chapter VII). McCalla (1940) showed by a series of quantitative experiments, that an actual rapid exchange of all types of cations could take place between the bacterial cell and surrounding medium. Non-specific competitive antagonism may then be regarded as an ion-exchange phenomenon in many cases.

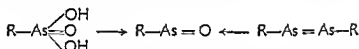
a highly reactive sulphydryl group, suggested to Voegtlin that arsenicals might be acting by combination with glutathione or other similar sulphydryl compounds essential to the life of the cell. He was able to show that trypanosomes contained free sulphydryl groups and that sodium thioglycollate ($\text{SH} \cdot \text{CH}_2\text{COONa}$), cysteine ($\text{SH} \cdot \text{CH}_2 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$) and glutathione antagonised the arsenoxide inhibition of motility of trypanosomes *in vitro*. *In vivo*, the injection of sulphydryl compounds one minute before injection of arsenoxide was found to slow considerably the rate of destruction of trypanosomes; the effect was not permanent, but the decline in arsenoxide-antagonistic action was found to coincide with a decline in the concentration of injected thiol compound in the blood. The oxidised forms of the sulphydryl compounds such as cystine or dithioglycollate showed comparatively little arsenoxide-antagonistic action. Sulphydryl compounds were found to lower the toxicity of arsenoxides for animals as well as for trypanosomes; thus, after administration of a lethal dose of arsenoxide, the life of an animal could be prolonged for several days by injection of antagonist. Voegtlin concluded that arsenic in the trivalent form is a specific poison affecting the SH groups of the protoplasm.

This view has been amply confirmed and extended during the intervening years. The bactericidal action of mercuric chloride had long been known to be reversed by treating the poisoned organisms with hydrogen sulphide or ammonium sulphide (Geppert, 1889; Chick, 1908). Fildes (1940a) showed that sulphydryl compounds such as glutathione and cysteine also antagonised the bactericidal effect of mercuric chloride. Mapharsen has been shown to possess antibacterial action comparable to that of mercuric chloride (Albert, Falk and Ruhho, 1944), and its bacteriostatic effect is also antagonised by sulphydryl compounds. Pentavalent arsenicals do not possess similar bacteriostatic properties.

Recently it has been found that both the trypanocidal action and the systemic toxicity for animals of trivalent antimonials such as tartar emetic and antimony thioglycollate are antagonised by cysteine. The toxicity of pentavalent

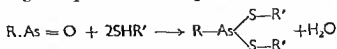
forms of life, including the animal host. Probably the toxic action resides in the metallic portion of the molecule, while the organic "tail" influences distribution and specificity.

Much of the credit for the development of a satisfactory theory of the mode of action of these drugs is due to Voegtlin, but the possibility that arsenicals might be toxic because of their affinity for mercapto groups had been suggested earlier by Ehrlich (1909). Voegtlin concluded that organic arsenicals were immediately toxic only in the arsenoxide form. During the considerable latent period before development of trypanocidal activity, atoxyl and arsphenamine were slowly converted by the tissues of the host to the arsenoxide form (Voegtlin, Dyer and Leonard, 1923).

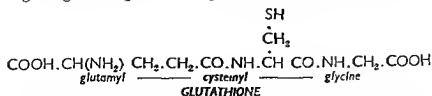


This view has recently been supported by careful analytical work on the excretion of pentavalent and trivalent phenyl arsenoxides after injection into rabbits. Although the amount of trivalent phenyl arsenoxide excreted after injection of the pentavalent compound was small, it was sufficient to account for the toxicity of the latter on the theory that it must be reduced in the body before producing its lethal effect (Crawford and Levvy, 1947).

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had shown that it was widely distributed in living tissues. This ubiquity, combined with the existence in glutathione of

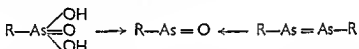
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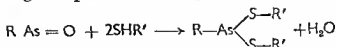
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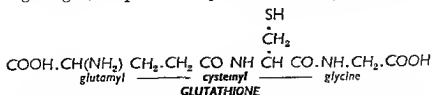


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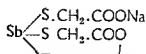
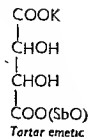
a and b). This suggests that arsenoxides may act directly by combination with enzyme proteins rather than by depriving the cell enzymes of essential metabolites.

If arsenoxides act *in vivo* by combining with the essential groups of "SH enzymes," it may well be asked why they are capable of destroying trypanosomes and other pathogens in the living animal, without at the same time inhibiting the essential "SH enzymes" of the host. Some enzymes, although possessing sulphydryl groups, are completely unaffected by concentrations of arsenoxide which inhibit such sensitive enzymes as yeast alcohol dehydrogenase, urcase, hexokinase and phosphoglyceraldehyde dehydrogenase. The selective destruction of trypanosomes may be also attributed to selective distribution of trypanocidal drugs, which are, however, not entirely without toxic action for the host. Eagle and Magnuson (1944) have found *in vitro* a general correlation between the trypanocidal activities of a wide range of phenylarsenoxides and the amounts of drug taken up by trypanosomes (Table 14). Selective distribution *in vivo* is, however, only an end-result of a number of variable factors (see Chapter VII).

When two types of cells metabolise substrates by the same pathway it does not follow that the enzymes catalysing intermediate reactions are necessarily identical. Alcohol oxidase of liver catalyses the same reaction as alcohol oxidase of yeast, but the former enzyme is not inhibited by iodoacetamide or arsenoxide while the latter is highly sensitive, i.e. is an "SH enzyme." The particularly high rate of carbohydrate metabolism of some trypanosomes is suggestive. Several of the reactions of glycolysis, pyruvate oxidation and carbon dioxide fixation are catalysed by "SH enzymes," and readily inhibited by arsenoxides. Only those species of trypanosome which have a high rate of carbohydrate metabolism can be successfully destroyed *in vivo* with arsenical drugs. The selective action of trypanocidal arsenicals may therefore be partly attributable to the relatively greater importance of "SH enzymes" in parasite than in host.

In addition to arsenoxides and iodoacetamide, numerous other organic molecules may react readily with the active

antimonials is not affected (Chen, Geiling and MacHatton, 1945).

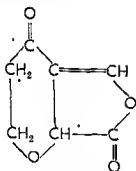


Sodium antimony thio glycollate

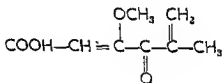
It is firmly established, then, that the toxic effect of metal complexes upon micro-organisms is antagonised by naturally-occurring sulphydryl compounds, and it is tempting to suggest with Fildes (1940a) that the organometallic compounds are toxic because they deprive cells of their essential sulphydryl-containing metabolites. Another, and we believe more probable explanation, can be profitably considered. As shown by Cohen, King and Strangeways (1931), the thioarsenites are largely hydrolysed in weak solution, and it seems improbable, if this is so, that the low concentration of trivalent arsenical reaching a pathogen *in vivo* would deprive it of any large percentage of the available glutathione or cysteine.

Arsenoxides inhibit the respiration of kidney, liver, testis, rat sarcoma and yeast, as well as trypanosomes and other pathogenic organisms; the inhibition is reversed in each case by glutathione (Voegtlin, Rosenthal and Johnson, 1931). Arsenoxides and glutathione have the same effect on the motility and viability of trypanosomes as they have on respiration. Trivalent organic arsenicals are bound by proteins which give a positive nitroprusside test, but do not combine with proteins which give no nitroprusside test (Rosenthal, 1932). We have already discussed in Chapter IV the importance of sulphydryl groups for enzymic activity. Some enzymes, known as "SH enzymes," have been shown to possess in the undenatured state several exposed sulphydryl groups which are absolutely essential for enzyme activity; such enzymes give a positive nitroprusside test. About thirty "SH enzymes" are now recognised, among them several concerned with carbohydrate metabolism (Barron and Singer, 1945

Geiger (1946) found that, although in general, quinones were less active against Gram-negative bacteria than Gram-positive, reversal by thiols was only effected in the case of Gram-negative organisms. He concluded that the activity against Gram-negative organisms was associated with an unsubstituted position ortho to the carbonyl groups, presumably necessary for combination with sulphydryl groups. No specific structure in the quinone molecule was necessary for activity against Gram-positive organisms, where it appeared that sulphydryl groups were not specifically attacked. In the case of hydroquinones, antagonism by thiols was also noted only with Gram-negative organisms. The reaction of thiols with quinones is an example of a general reaction, the addition of thiol to $\alpha : \beta$ -unsaturated ketone. Other substances, both natural and synthetic, containing the $\alpha : \beta$ -unsaturated ketone grouping have been found to possess antibacterial action which was antagonised by cysteine. The antibiotics clavacin and penicillic acid were found to abolish the nitroprusside reaction of



Clavacin



Penicillic acid

cysteine, showing that they reacted with the sulphydryl group, and their antibacterial actions were fully antagonised by thiols. The synthetic ketone acrylophenone showed similar antibacterial action, also antagonised by thiols (Geiger and Cohn, 1945; Cavallito, Bailey, Haskell, McCormick and Warner, 1945; Rinderknecht, Ward, Bergel and Morrison, 1947).

In Chapter IV we discussed the reversibility of enzyme inhibition, and showed that the toxic action of an inhibitor was dependent on the dissociability of the inhibitor-enzyme

hydrogen of "SH enzymes." Quinones possess antibiotic properties which have been attributed to their ability to react

TABLE 14

The trypanocidal activity of arsenicals in relation to their binding by trypanosomes

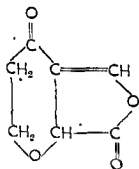
(Final arsenic concentration of medium was 1.66 $\mu\text{g./c.c.}$)

Compound. (All compounds are phenylarsenoxides R-C ₆ H ₄ AsO unless otherwise stated.) R =	Relative trypanocidal activity <i>in vitro</i> (molar referred to phenylarsenoxide as 100.	Average concentration in trypanosomes (mgs. As per cent)
p-SO ₂ H	0.06	0.41
p-CONHCH ₂ COOH	0.22	0.36
p-SO ₂ NHCH ₂ CONH ₂	1.4	0.68
p-CH ₂ CONHCH ₂ CONH ₂	1.5	1.4
p-CH=CHCOOH	2.0	0.2
3-NHCOCH ₂ -4-OH	3.0	2.1
p-OCH ₂ COOH	4.5	1.5
p-CH ₂ COOH	4.7	1.6
p-CONHCH ₂ CONH ₂	15.0	5.7
p-OCH ₂ CONH ₂	26.0	6.8
3-NH ₂ -4-OH	27.0	6.5
3-OH-4-NH ₂	30.0	6.9
p-NHCOCH ₂ NH ₂	31.0	3.6
p-SO ₂ N(C ₂ H ₅) ₂	35.0	7.4
p-NHCONH ₂	35.0	5.3
p-SO ₂ NH ₂	30.0	5.5
p-CONH ₂	45.0	7.7
3-NH ₂ -4-CONH ₂	52.0	7.6
p-(CH ₂) ₃ COOH	54.0	6.9
3-NH ₂ -4-Cl	59.0	8.7
m-OH	66.0	8.2
2-OH-5-AsO-azobenzene	71.0	9.6
1-naphthylarsenoxide	79.0	10.4
2, 4-diCl	80.0	9.5
p-Cl	90.0	7.2
o-CH ₃	91.0	9.5
o-Cl	92.0	9.3
m-Cl	95.0	10.3
phenylarsenoxide	100.0	9.7
p-CH ₃	102.0	10.0
2-naphthylarsenoxide	105.0	10.2

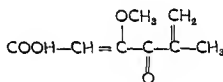
From Eagle and Magnuson (1944).

with sulphydryl groups (Colwell and McCall, 1945). This interpretation, although supported by the reversal of certain cases of quinone bacteriostasis by thiols such as cysteine or thioglycollate, cannot be considered as entirely satisfactory.

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The trypanocidal activity of arsenicals in relation to their binding by trypanosomes

(Final arsenic concentration of medium was 1.66 $\mu\text{g/c.c.}$)

Compound. (All compounds are phenylarsenoxides $\text{R-C}_6\text{H}_4\text{AsO}$ unless otherwise stated.) R =	Relative trypanocidal activity <i>in vitro</i> (molar) referred to phenylarsenoxide as 100.	Average concentration in trypanosomes (mgs. As per cent.)
$p\text{-SO}_2\text{H}$	0.06	0.41
$p\text{-CONHCH}_2\text{COOH}$	0.22	0.36
$p\text{-SO}_2\text{NHCH}_2\text{CONH}_2$	1.4	0.68
$p\text{-CH}_2\text{CONHCH}_2\text{CONH}_2$	1.5	1.4
$p\text{-CH=CHCOOH}$	2.0	0.2
$3\text{-NHCOCH}_2\text{-4-OH}$	3.0	2.1
$p\text{-OCH}_2\text{COOH}$	4.5	1.5
$p\text{-CH}_2\text{COOH}$	4.7	1.6
$p\text{-CONHCH}_2\text{CONH}_2$	15.0	6.7
$p\text{-OCH}_2\text{CONH}_2$	26.0	6.8
$3\text{-NH}_2\text{-4-OH}$	27.0	6.5
3-OH-4-NH_2	30.0	6.9
$p\text{-NHCOCH}_2\text{NH}_2$	31.0	3.6
$p\text{-SO}_2\text{N(C}_2\text{H}_5)_2$	35.0	7.4
$p\text{-NHCONH}_2$	35.0	5.3
$p\text{-SO}_2\text{NH}_2$	30.0	5.5
$p\text{-CONH}_2$	45.0	7.7
$3\text{-NH}_2\text{-4-CONH}_2$	52.0	7.6
$p\text{-(CH}_2)_3\text{COOH}$	54.0	6.9
$3\text{-NH}_2\text{-4-Cl}$	69.0	8.7
$m\text{-OH}$	66.0	8.2
$2\text{-OH-5-AsO-azobenzene}$	71.0	9.6
1-naphthylarsenoxide	79.0	10.4
$2, 4\text{-diCl}$	80.0	9.5
$p\text{-Cl}$	90.0	7.2
$o\text{-CH}_3$	91.0	9.5
$o\text{-Cl}$	92.0	9.3
$m\text{-Cl}$	95.0	10.3
phenylarsenoxide	100.0	9.7
$p\text{-CH}_3$	102.0	10.0
2-naphthylarsenoxide	105.0	10.2

From Eagle and Magnuson (1944).

with sulphydryl groups (Colwell and McCall, 1945). This interpretation, although supported by the reversal of certain cases of quinone bacteriostasis by thiols such as cysteine or thioglycollate, cannot be considered as entirely satisfactory.

acidic nucleic acid (Massart *et al.*, 1947). The large anion of sodium dodecyl sulphate can antagonise the bacteriostatic action of streptomycin (Valko and DuBois, 1944), but in this case, there can be no question of the dodecylsulphate ion acting nutritionally.

Quantitative aspect of combination of metals with cells and enzymes

Heavy metals produce lethal effects on living cells at extremely low concentrations. When first discovered, this general lethal action was considered so remarkable that it was given the special name "oligodynamic action" and many elaborate theories were advanced to explain its nature (for references see Buchanan and Fulmer, 1928). The low concentrations are deceptive, however, since living cells suspended in dilute solutions of metallic salts fix quite large quantities of metal before lethal action is produced. Quantitative measurement of the fixation of mercuric chloride by yeast (Herzog and Betzel, 1911) showed that there was a considerable concentration of mercury in the cell at the time of death. *Spirogyra* were killed by silver at a concentration of 3 γ per litre, but the killed organisms were found to have fixed up to 60 γ silver per gm. dry weight (Freundlich and Söllner, 1928). Quantitative measurement of the fixation of mercuric chloride by staphylococci also indicated that at the time of death there was a considerable concentration of metal in the cell (Liese and Mendel, 1923). A direct stoichiometric relation was found between the number of titratable thiol groups of *E. typhosa* and the amount of mercurial antiseptic required to sterilise cell suspensions. If sufficient time of contact were allowed, only one quarter of the bacterial thiol groups had to be blocked to effect complete sterilisation (Loureiro and Lito, 1946). The action of metals on cells is a double effect, firstly rapid fixation which is reversible, and secondly slow irreversible injury which can probably be attributed to general protein denaturation. The initial reversible fixation resembles very closely the action of heavy metals on "SH enzymes." Thus, Sumner and Myrbäck (1930) found that

complex relative to that of the antagonist-enzyme or antagonist-inhibitor complex. The effectiveness of 2:3-dimercaptopropanol (B.A.L.) in antagonising war gases, such as lewisite, which combine with "SH enzymes," was shown to be due to formation of highly stable non-dissociating ring compounds with the poisons. The stability of these compounds is such that B.A.L. can reverse the toxic and vesicant effect of lewisite for at least an hour after contamination of the skin, after which time irreversible changes presumably occur. B.A.L. can also counteract the toxic effect of arsenical drugs on animals (Stocken, Thompson and Whittaker, 1947).

The failure of B.A.L. to reverse the toxic reaction to lewisite if applied to the skin more than one hour after lewisite, is characteristic of many antagonists both *in vitro* and *in vivo*. We showed that enzymes may be reactivated after poisoning with mercury or arsenicals, provided the antidote is added soon enough after the poison. If bacteria or other unicellular organisms are brought into contact with dilute mercuric chloride, growth and reproduction are immediately inhibited, but provided cells are not left too long in contact with mercuric chloride, growth is resumed when mercury is removed by hydrogen sulphide or glutathione (Chick, 1908; Fildes, 1940a).

It will be noted that the thiol-antagonism of organometallic compounds and heavy metals does not involve competitive inhibition as defined at the beginning of this chapter. Competitive inhibition is regarded as occurring when two substances *which cannot interact chemically* compete for a common centre on an enzyme. Thiols antagonise heavy metals, not by competing with them, but by a chemical combination. The reversal of acridine bacteriostasis by nucleate (McIlwain, 1941a) and the antagonism of stilbamidine and pentamidine bacteriostasis by the same type of compound (Bichowsky, 1944) may be, as suggested by McIlwain, due to the ability of nucleate to function as an essential metabolite. The effect can be equally well explained on the basis of chemical combination of basic drug with

relatively insensitive to the sulphonamides. This effect was traced to the fact that the organisms in question require carbon dioxide for growth; this can be supplied from arginine by decarboxylation. When the arginine in the medium is exhausted, carbon dioxide is obtained from other sources. This utilisation of carbon dioxide is inhibited by sulphanilamide, but not by sulphapyridine or sulphathiazole, and, in the absence of carbon dioxide and arginine, the organism is relatively susceptible to sulphanilamide, but the sulphapyridine and sulphathiazole resistance are unchanged.

The study of antagonists has led also into the field of drug resistance. It has been found possible to develop organisms resistant to a drug by growth in a medium from which the drug antagonist is omitted; in other words, resistance may be developed by training an organism to be independent of the essential metabolite of which it would be deprived by addition of drug. Thus, *Corynebacterium diphtheriae* developed resistance to pantooyl taurine when trained to grow in pantothenic acid-deficient media (McIlwain, 1943b). The inhibitory effect of indole-3-acetic acid on growth of *Strep. faecalis* (antagonised by tryptophan) was not apparent when the organism was trained to grow on ammonia instead of amino acids (Periman, 1946).



1. Antagonism by amino acids
Antagonism by drugs, can be overcome by + antiserum

(1) non specific competitive Antagonism

3. False non antagonism

(ii) competitive antagonism

purified urease was inactivated reversibly by 1 gm. atom of silver per 40,000 g. of enzyme, but a slow secondary irreversible combination with a further 10 gm. atoms of silver could take place. As noted already, denaturation of urease and other enzymes unmasks additional sulphydryl groups, so that the course of the reaction can be regarded as rapid combination of metal with exposed essential sulphydryl groups, followed by slow denaturation of enzyme with accompanying increase in power to bind metal. A similar effect can be observed with arsenic poisoning of trypanosomes. Living trypanosomes fix arsenic reversibly; after death, cells fix about ten times as much arsenic (Reiner, Leonard and Chao, 1932). The initial reversible combination of arsenic with essential groups of "SH enzymes" prevents cell multiplication or metabolism; this causes death of the cell, protein denaturation and unmasking of additional sulphydryl groups.

Antagonism by amino acids

Various cases have been reported in which the antibacterial effects of drugs other than sulphonamides are strongly antagonised by certain amino acids. These results are difficult to interpret in terms of cell metabolism. Amino acids are essential building blocks for proteins, and it may be that their presence in the medium eliminates the need for certain synthetic reactions which are blocked by growth-inhibitory drugs. Methionine antagonism of sulphonamides has already been discussed. Woolley (1946a) reported antagonism of phenylpantothenone by amino acids; histidine was the most active, and glutamic acid next. Penicillin-insensitive Gram-negative bacilli were found by Schwartzman (1946) to be sensitive to the drug in salt-glucose medium. Penicillin antagonism, in this medium, was shown by dicarboxylic mono-amino acids, and by arginine, histidine, hydroxyproline and cystine. Resistance of organisms to penicillin could be changed by repeated culture in the presence of antagonistic amino acids.

Arginine was found by Gale (1945) to have an antagonistic effect on sulphanilamide for certain streptococci which are

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Variation by adaptation.—Enzyme adaptation was fully investigated by Karstrom (1938), who distinguished between "adaptive" enzymes which appeared in response to contact of the cell with a suitable substrate, and "constitutive" enzymes which were always present in the cells of a given strain irrespective of the composition of the medium. Karström was able to show that organisms grown for a few hours in the presence of sugars which they did not normally ferment, adapted themselves to ferment these sugars. An example of

TABLE 15

Adaptation of Betacoccus arabinosaceus to ferment sugars
(+ = fermentation; 0 = no fermentation)

Betacoccus grown in presence of	Sugars subsequently fermented					
	Glucose, Fructose, Mannose	Galactose	Arabinose	Sucrose	Maltose	Lactose
Glucose .	+	0	0	(+)	0	0
Galactose .	+	+	0	+	0	0
Arabinose .	+	0	+	+	0	0
Sucrose .	+	0	0	+	0	0
Maltose .	+	0	0	+	+	0
Lactose .	+	+	0	+	0	+
No carbo- hydrate	+	0	0	+	(+)	0

From Karstrom (1938).

the adaptation of *Betacoccus arabinosaceus* (*Leuconostoc mesenteroides*) to ferment various sugars is given in Table 15.

It seems unlikely that completely new enzymes are elaborated by the cell in a few hours in response to external stimuli, and the difference between constitutive and adaptive enzymes is probably quantitative rather than qualitative. Contact with a suitable substrate would not necessarily result in formation of a new enzyme, but could increase the rate of synthesis or efficiency of utilisation of an enzyme already present in small amounts, or decrease its rate of destruction.

CHAPTER VI

DRUG RESISTANCE

Variation

THE enzymic balance of the bacterial cell can undergo considerable variation in response to changes in environment. *Escherichia coli* produces up to 20 times more invertase when it is grown in a medium containing sucrose than when the medium contains glucose (Karstrom, 1938). As a result of successive subculture under suitable conditions, an organism may develop a capacity to metabolise substances which were previously toxic to it, or it may develop the ability to synthesise an essential metabolite which it formerly required as an addition to the basal medium (Fildes, Gladstone and Knight, 1933).

In general, two types of enzymic change are recognisable, (1) a rapid development of enzyme activity without the necessity of cell division, (2) and a much slower alteration in metabolic pattern which can only be demonstrated over a series of generations. Rapid variation in enzymic balance in response to the presence of a given substrate in the culture medium is usually equally rapidly reversible. This type of variation we shall define as variation by enzyme adaptation. Variations which can only be observed after a series of subcultures are of a more permanent nature. The change has been brought about by a slow process of selection of variants which differ enzymically from the parent cells in such a way that they are better suited to the new environment. Eventually they are present in preponderant amounts, having overgrown the other cells of the culture which are less suited to the environment. This type of variation we shall define as variation by selection. Enzymic variation produced by selection during growth of successive generations may be permanent even in the absence of the selective mechanism, or it may be lost slowly over a number of subcultures.

Variation by adaptation.—Enzyme adaptation was fully investigated by Karstrom (1938), who distinguished between "adaptive" enzymes which appeared in response to contact of the cell with a suitable substrate, and "constitutive" enzymes which were always present in the cells of a given strain irrespective of the composition of the medium. Karstrom was able to show that organisms grown for a few hours in the presence of sugars which they did not normally ferment, adapted themselves to ferment these sugars. An example of

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Maltose .	+	0	0	+	+	0
Lactose .	+	+	0	+	0	+
No carbo- hydrate	+	0	0	+	(+)	0

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THE BASIS OF CHEMOTHERAPY

The work of Mirick (1943) on an adaptive enzyme of certain soil bacilli illustrates the general characteristics of adaptive enzymes. The bacilli grown in the absence of *p*-aminobenzoic acid (P.A.B.A.) possessed a small but measurable capacity to oxidise P.A.B.A. (see Fig. 25). When cells were grown in media containing P.A.B.A. their capacity to oxidise the acid increased rapidly in proportion to the concentration of

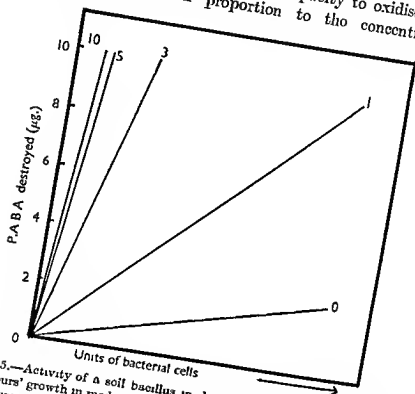


FIG. 25.—Activity of a soil bacillus in destruction of P.A.B.A. after twelve hours' growth in media containing varying amounts of P.A.B.A. as sole source of organic nitrogen. Figures represent µg. of P.A.B.A. per ml. of growth medium. (Mirick, 1943).

P.A.B.A. in the medium, but subculture in another medium containing no P.A.B.A. resulted in a rapid loss of activity. The acquisition of the power to oxidise P.A.B.A. was not dependent upon cell division, since shaking a washed suspension of non-adapted cells for one hour with P.A.B.A. in phosphate buffer resulted in a marked increase of enzymic activity.

The occurrence of enzyme adaptation without cell division has been demonstrated with other organisms and other enzymes, thus confirming that it is a process independent of

DRUG RESISTANCE

natural selection (Stephenson, 1939; Dubos, 1940; Gale, 1943; Spiegelman, Lindegren and Hedgecock, 1944).

The rate of adaptation depends not only on the nature of the culturo medium on which the inoculum has been grown, but also upon the age of the cells. As is indicated in Fig. 26, *Strep. lactis* cells from a one-hour culture adapted themselves to ferment galactose in one hour, whereas cells taken from the same stock culture after four hours required nine hours to adapt themselves to ferment galactose. The one-hour cells

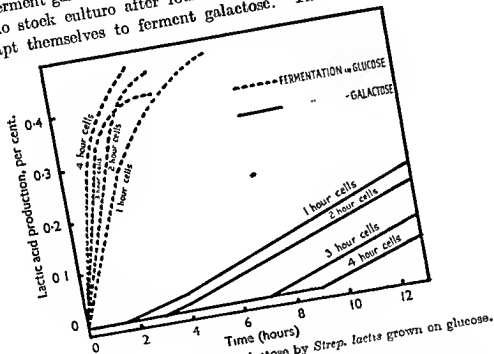


FIG. 26 — Adaptation to ferment galactose by *Strep. lactis* grown on glucose. (Hegarty, 1939).

were just coming out of the lag phase and the four-hour culture was past the middle of the logarithmic phase of growth (Hegarty, 1939).

Enzyme adaptation is a direct response to environment, and its function may be largely to counteract or utilise unfavourable external conditions. Thus, adaptive enzymes may act in such a way as to restore the pH of a medium to near neutrality, as is the case with the deaminases and decarboxylases of *Escherichia coli* (Gale and Epps, 1942); or they may act as detoxicating mechanisms converting unsuitable metabolites into utilisable intermediates.

For maximum enzymic adaptation, it is often sufficient simply to expose the organism to a suitable concentration of substrate, but in other cases the necessity for accessory factors has been demonstrated. Tyrosine decarboxylase was found to be produced in optimal amounts only when pyridoxin and nicotinic acid as well as tyrosine were added to a basal medium (Bellamy and Gunsalus, 1944). The significance of this observation became evident later when pyridoxin was shown to act as coenzyme for amino acid decarboxylases (Gunsalus and Bellamy, 1944a). The necessity for nicotinic acid in this adaptation may also be related to its coenzyme function.

Dubos (1940) suggests that although production of new enzymes may occur in the absence of cell division, it must always involve synthesis of new protoplasm. The adaptation of *Saccharomyces cerevisiae* to galactose fermentation has been found to be dependent, in the absence of other carbohydrate, on the oxidation of galactose itself, which probably provided the necessary energy for enzyme adaptation (Spiegelman, 1945b; Reiner and Spiegelman, 1947; Spiegelman, Reiner and Cohnberg, 1947). Adaptation has not been observed where metabolism is not possible. An interesting suggestion as to the origin of adaptive enzymes has been made by Monod (1943, 1944, 1945) and by Spiegelman (1946). These authors have obtained evidence that many enzymes concerned with the metabolism of chemically-related substrates derive from a common pre-enzyme. Some substrates may have greater affinity for the pre-enzyme and will be able to displace other substrates. This principle is seen at work in the adaptation of yeast to various sugars. In the absence of an exogenous source of nitrogen, adaptation to galactose lowers the glucosylase content of yeast cells. If a culture fully adapted to maltose is adapted to galactose, the increase in its galactosylase activity is associated with a sharp drop in maltase activity (Spiegelman, 1946).

Ease of adaptation varies considerably and in some cases actually requires conditions compatible with cell division. The amino acid decarboxylases of *Escherichia coli* are formed optimally only under conditions when cell division can occur,

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may go on for several years. In some cases, however, there has been regional lymph node involvement. Delarue and Graham observed areas of the tumor in which the cells were growing wildly in solid clumps and cords in a loose fibrous stroma with no attempt at alveolar formation, and in their case there was recurrence four years after lobectomy. Distant metastases have been described, but none of these cases is completely acceptable.

What, then, are we to say about the malignancy of the tumor? Surely it is essentially a matter of words. As with carcinoid of the appendix and adenoma of the bronchus, the neoplasm may be regarded either as benign with occasional leanings to malignancy as shown by spread to lymph nodes (pulmonary adenomatosis), or as malignant but to a very slight degree (alveolar-cell carcinoma). It would seem advisable to adopt a nonpartisan position and take refuge in the term "alveolar-cell tumor."

Even more contentious is the question of the origin of the tumor, but it is of academic rather than practical significance. A never-ending battle rages among the histologists as to whether the pulmonary alveoli have a lining, and if so, whether or not it is epithelial. To the pathologist the matter appears simpler. He knows that the alveoli become lined with cuboidal cells in a variety of conditions in which respiratory function is diminished, e.g., chronic passive congestion, lipoid pneumonia, chronic interstitial pneumonia, etc. This he calls epithelization or fetalization of the alveoli. It is a return to the early fetal state of the lung, in which the alveoli are lined by cuboidal cells derived from the endodermal buds that represent the developing bronchi. If these cells persist in later life in flattened and rudimentary form, they would provide the natural starting point for such a condition as adenomatosis. Herbut and other writers believe that the alveolar cells in this disease represent an extension of the bronchiolar epithelium into the alveoli, much as is seen in certain cases of bronchiectasis. This view is expressed in categorical fashion by Fried in these words: "The cells in diffuse intra-alveolar (alveolar cell) cancer should be looked upon not as mutation of the so-called alveolar epithelium but as a widely distributed cana-

licular metastasis from an invisible (with the naked eye) or overlooked cancer of the bronchus." This possibility cannot be denied, but it fails to fit in with the multicentric nature of the tumors, nor do the cells of the tumor resemble those of the bronchial mucosa. All in all, origin from alveolar epithelium seems to be the most satisfying ex-



Fig. Introd. 2-6. Region invaded by tumor of the thoracic inlet (From B. Ray, permission *Surg Gynec & Obst* 67 590, 1938.)

planation. (See Chapter 29 for a detailed discussion of alveolar-cell carcinoma.)

Tumor of the Thoracic Inlet

This is the tumor that is responsible for the production of the Pancoast syndrome. It is not a specific entity (Figure Introd. 2-6).

The tumor may be intrapulmonary or extrapulmonary. The intrapulmonary tumor is an apical carcinoma arising from a terminal bronchiole. The extrapulmonary neoplasm may be a secondary carcinoma at the root of the neck, carcinoma of the thyroid, neurogenic sarcoma, etc. Occasionally the tumor may be primary, yet without evident origin from any organ in the neighborhood. These



Fig. Intro. 2-7. A. Adenoma of bronchus (gross), B. Adenoma of bronchus (microscopic) (From W. Boyd, *Pathology of Internal Diseases*, 1950, courtesy Lea & Febiger.)

cases are believed to arise from an embryonic rest.

Adenoma of Bronchus

Like bronchogenic carcinoma, bronchial adenoma is a modern disease—as modern as the bronchoscope. Fortunately, it has not yet been attributed to cigarette smoking. It is much rarer than carcinoma. The sex incidence differs. In twenty-six cases analyzed at the Toronto General Hospital [8] there were equal numbers of males and females, whereas the incidence of carcinoma was 91 per cent male and 9 per cent female.* The average age at which the patient was seen was ten years younger than in carcinoma. In seventeen patients the tumor was on the right side, in only nine on the left.

The tumor is usually situated in or near a main bronchus. At first it presents a wart-like prominence (Figure Intro. 2-7) but with the passage of time it may grow in two directions. When growth is mainly into the lumen the tumor becomes pedunculated, "hanging" (in Frid's happy phrase) "by its constricted neck like the clapper of a bell."

Or the advance may be mainly outward, so that, like the iceberg, the greater part of its bulk may be invisible to the observer through the bronchoscope (Figure Intro. 2-8).

The microscopic picture varies to a degree seldom seen in adenomas in other organs. The epithelial cells—oval or round with large nuclei and scanty cytoplasm—are arranged in irregular masses, sheets, or cords separated by a delicate stroma rich in blood vessels. The appearance may be that of solid tubules, and may strongly suggest that of the fetal lung in an early stage of development (Figure Intro. 2-7B). The tumor cells may be separated from the surface epithelium by fairly dense

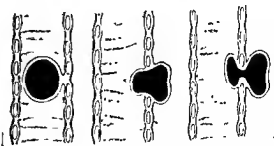


Fig. Intro. 2-8. Diagram showing differing locations of adenoma in the bronchial wall. (From H. Brunn and A. Goldman, *permission Surg. Gynec. & Obst.* 71:703, 1940)

* These and the following hitherto unpublished figures were kindly supplied by Dr. Delarue working under Dr. R. M. Jones.

fibrous tissue. Occasionally mesodermal elements such as cartilage and bone are encountered, this was so in three of Delarue's twenty-six cases. The overlying mucosa is intact, although it may undergo squamous metaplasia. This is another striking difference from bronchial carcinoma.

The origin of the tumor is a matter of dispute, some writers favoring the basal cells of the mucosa, others the bronchial glands. In a neoplasm large enough to manifest itself clinically it is impossible to determine the exact cell of origin, nor does it really matter. Womack and Graham believe that the adenoma arises from embryonal bronchial buds

have developed full-blown features of malignancy the identity of the original tumor is lost." The question is very similar to that of carcinoid tumor of the appendix, which is usually benign though locally invasive, but may occasionally spread to the regional nodes, and very rarely to distant organs. It is essentially a matter of words. The adenoma may be regarded as a benign tumor with some tendency toward malignancy, or as a malignant tumor of such low grade that it usually remains localized. But it is surely a mistake to speak of an adenoma as malignant merely because after a long time it may show malignant characteristics. One has only to think of

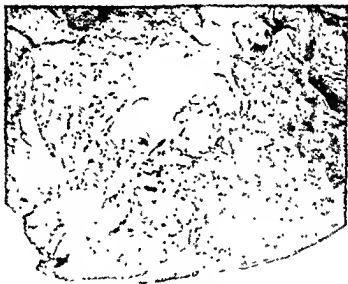


Fig. Introd. 2-9. Invasive bronchial adenoma.

that have failed to develop into normal structures. The occasional presence of mesodermal elements suggests to them a developmental origin. The resemblance to a human fetal lung in the sixteenth week of development is sometimes remarkable.

The question of malignancy is unsettled. The tumor, although usually circumscribed, may invade the surrounding lung (Figure Introd. 2-9). Involvement of the regional lymph nodes sometimes occurs. In very rare cases minute metastatic tumors have been reported. It is evident, therefore, that an adenoma has malignant potentiality and should be treated as such. Graham and Womack [16] go farther and state that the "majority of these tumors become malignant. After they

adenoma of the thyroid and its occasional development into carcinoma to see the truth of this statement. That a true bronchogenic carcinoma seldom if ever originates as an adenoma is shown by the very striking sex difference, the distinct age difference, and the great difference in the duration of premonitory symptoms.

Hamartoma of the Lung

A rare benign tumor of the lung is the hamartoma, so called because it is supposed to be the result of abnormal development of the bronchial anlage (hamartion: a bodily defect). Its position is in striking contrast to the bronchial adenoma, for it is peripheral, often subpleural. In most cases the chief con-

stituent is cartilage, with occasional bone formation. There may be epithelial and mucous glands and cysts. It usually causes no symptoms and is discovered on routine x-ray examination or at autopsy. McDonald, Harrington, and Clagett [31] reported twenty-three cases; twenty of the tumors were found at autopsy and three were removed surgically.

Pleural Mesothelioma

Tumors of the pleura may be localized or diffuse. The *localized* tumors arise from the

involvement of the pleura, and brusquely dismiss all the reported cases as insufficiently studied. With this view, the author is in entire disagreement. The lack of agreement, as Klemperer and Rabin [25] remark, is due to the wide variations in the microscopic appearance, some of the tumors being epithelial in character, some fibroblastic, and others either both or neither. The tumor, therefore, may present a picture suggesting either carcinoma or sarcoma. The combination of connective tissue and epithelial elements is



Fig. Introd. 2-10. Pleural mesothelioma showing invasion of the lung

subserous connective tissue of either the visceral or parietal pleura. The most important member of the group is the so-called giant sarcoma of the visceral pleura, which is of very slow growth and neither infiltrates nor metastasizes, so that it may attain an enormous size and fill the entire pleural cavity. In spite of its benign behavior, it has the microscopic appearance of a fibrosarcoma.

The *diffuse* tumor arising from the mesothelial lining of the pleura has long been, and still is, the subject for sharp differences of opinion. Some authors, of whom Willis [43] is the chief modern representative, deny the very existence of the condition, holding that all such tumors are examples of metastatic

characteristic of these growths. Postoloff, in reporting a case from my laboratory, points out that the most valuable single procedure is a thorough gross examination to rule out other possible primary tumors.

The gross appearance is highly characteristic, for there is a diffuse thickening of the pleura that may extend over a considerable area or even the entire lung, and may be over 1 cm. in depth, as might be expected in a tumor arising from surface cells. Both layers of the pleura may be involved. Invasion of the lung may be entirely missing, but more often the tumor involves the septa and parenchyma, producing irregular nodules or masses that may suggest a possibility of

bronchogenic carcinoma (Figure Introd. 2-10.) Pleural effusion is common, at first serous and later hemorrhagic. Metastases may appear in the bronchial, mediastinal, or cervical lymph nodes and in the liver and spleen.

Pulmonary Arteriovenous Aneurysms

It may be questioned whether this condition should be considered in a book on neoplasms. The justification for doing so is that one of the alternative names is pulmonary cavernous hemangioma, and that surgical treatment is attended by brilliant results.

The salient features of the disease are expressed so clearly and concisely in a paper by Pugsley in an analysis of five cases in the Toronto General Hospital that I take the liberty of transcribing the opening paragraph of his article. (Parenthetically it may be remarked that the report of the first case to be cured by pneumonectomy was made by Hepburn and Dauphinee of the same hospital in 1942, the operation being performed by Shenstone and Janes.)

Arteriovenous aneurysm of the lung is a rare anomaly of the pulmonary circulation in which a large vascular cavity, incompletely divided by septa, is in direct communication with one or two dilated branches of the pulmonary artery and vein. A proportion of the venous blood in the pulmonary artery passes through the aneurysmal sac to the pulmonary vein and, therefore, fails to be aerated in the lungs; consequently the blood is returned to the systemic circulation incompletely saturated with oxygen. The arterial anoxia gives rise to dyspnea on effort, cyanosis, clubbing of the fingers, and a secondary polycythemia. When a young person presents the above combination of signs, without evidence of heart disease, and a radiograph of the chest reveals a discrete density in the lung, a pulmonary arteriovenous aneurysm should be suspected [37].

Little need be added to the above summary. About half of Pugsley's cases had cerebral symptoms such as dizzy spells, brief periods of inability to speak, or attacks of unconsciousness or convulsions. Telangiectasis of the skin or of the mucous membranes of the nose or oral cavity were present in 40 per cent of the cases. This association indicates a developmental defect in the formation of blood vessels in different parts of the body. Hayward and Reid suggest that this defect may have a hormonal basis, as indicated by

the presence of telangiectases during pregnancy and in cirrhosis of the liver, a condition in which there is interference with the normal breakdown of steroid hormones in the liver. Symptoms usually begin in the first or second decade. In the x-ray film there is a rounded, discrete density in the lung, with linear opacities connecting it with the hilus. An angiogram taken a few seconds after the injection of Diodrast will demonstrate filling of the pulmonary density.

The condition is slowly progressive and finally may incapacitate the patient. Death may occasionally result from rupture of the aneurysm into a bronchus or the pleural cavity. This indicates the necessity for surgical excision.

Hayward and Reid, by means of skilled dissection of the lesion injected with gelatin, have shown that the aneurysm, or telangiectasis as they prefer to call it, is a large cavity supplied by a greatly dilated pulmonary artery and drained by an equally dilated pulmonary vein. When the lung is sliced, these tortuous vessels are cut across, giving a multilocular appearance that has led to the mistaken diagnosis of cavernous angioma. The large lesion is merely an exaggeration of a more diffuse process, for they demonstrate and illustrate many small, dilated vessels scattered through the adjacent lung.

MEDIASTINAL TUMORS

The mediastinum is a complex structure containing a great variety of tissues. It is natural that an equal variety of tumors should have been reported. The most useful classification is to divide these tumors into those of the anterior mediastinum and those of the posterior mediastinum. Excluding lymphoblastomas of the mediastinal nodes (lymphosarcoma, reticulum cell sarcoma, Hodgkin's disease) and secondary tumors of these nodes, which will not be considered here, the neoplasms may again be divided into two great groups: the neurogenic tumors and the teratomas, which may be solid or cystic. The former group is almost always confined to the posterior, the latter to the anterior mediastinum. In addition to these, mention must be made of some additional types, including tumors of the thymus gland.

Neurogenic Tumors of the Mediastinum

These tumors are practically confined to the posterior mediastinum by reason of the fact that they nearly always arise from the posterior roots of the spinal nerves. Only two cases in the literature are reported as being

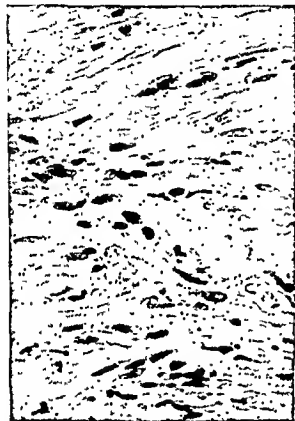


Fig. Introd. 2-11. Neurofibroma with elongated cells and nuclei. (X 320)

in the anterior mediastinum, but the writer has recently encountered at autopsy one tumor weighing 1,225 Gm. in that location. The tumor may be a neurofibroma (Figure Introd. 2-11) or a ganglioneuroma (Figure Introd. 2-12), also called a sympathicoblastoma because of its origin from ganglia in the sympathetic chain. The neurofibroma may be benign or malignant.

The neurofibroma is not a true tumor in the strict sense of the word, but rather a disorderly overgrowth of nerve tissue similar to that seen in the neurofibromatosis of von Recklinghausen's disease. The principal constituent is a long cell with a fusiform nucleus (Figure Introd. 2-11) which is derived according to Masson from the sheath of Schwann or neurilemma, and according to

Penfield from the perineurium or connective tissue investment; hence the names schwannoma, neurilemmoma, and perineural fibroma.

Teratoid Tumors of the Mediastinum

"It would be difficult to find in the adult human body a region of less intrinsic interest than that space between spaces known to



Fig. Introd. 2-12. Ganglioneuroma showing ganglion cells and nerve fibers (X 150) (From W. Boyd, *Pathology of Internal Diseases*, 1950, courtesy Lea & Febiger)

anatomists as the anterior mediastinum." This statement was made by Wilson in 1884. Other times, other ideas; for this "space between spaces" has now become of very great interest both to the thoracic surgeon and to the pathologist. Developmental tumors, solid and cystic, are confined to the anterior mediastinum. They are likely to manifest themselves first in adolescence or early adult life. One occurred in a stillborn infant. Evidence of intrathoracic pressure in early adult life should suggest the possibility of a teratoma. Although all the lesions are teratoid, it has become customary to reserve the term teratoma for the solid tumors and to speak of the cysts as dermoids. A convenient classification suggested by Hedblom [18] is into epider-

moids, dermoids, and teratomas. The *epidermoids* are cysts containing only derivatives of ectoderm, lined by squamous stratified epithelium, with glands in the dense fibrous wall (Figure Introd. 2-13) and filled either by milky fluid or sebaceous material often mixed with hair. The *dermoids* are cysts that have tissues of mesodermal as well as ectodermal origin. Thus, in addition to hair, epithelium, and glands, there are cartilage, bone, teeth, and muscle. The *teratomas* are solid tumors which, in addition to the above, contain tissues of endodermal origin, e.g., respiratory

that the tumors arise as the result of an abnormality in the development of the third and fourth branchial arches. Groups of cells separated in the early stage of development may be carried into the thorax by the normal descent of the heart and great vessels and there develop into tumors.

The tumor may be stationary, or may increase in size as the result of infection or malignant change. The latter, which is more common in the solid tumors, may take the form of squamous-cell carcinoma or adenocarcinoma. The symptoms are likely to begin



Fig. Introd. 2-13 Teratoid tumor of epidermal type ($\times 90$) Large mass of stratified epithelium to the left and alveolar epithelium to the right

and digestive tract structures. Laipply [27], in an analysis of 245 cases from the literature, found epidermoid cysts to be the commonest, followed at some distance by dermoid cysts and teratomas in equal numbers.

The precise origin of teratoid tumors has never been settled, although all sorts of suggestions, fantastic and otherwise, have been propounded, such as segregation of a blastomere, a misplaced sex cell, and even an extruded polar body. Why this should occur particularly in the anterior mediastinum has never been explained. The tumors are nearly always situated high in the superior mediastinum, and may be firmly attached to the pericardium and great vessels. The theory that appears best to fit in with the observed facts is that suggested as long ago as 1869, namely,

in early adult or middle life. Cough, especially in the recumbent position, is the most constant feature; there may be pain and dyspnea. The sputum may be blood-streaked and contain sebaceous or gelatinous material, mixed with hair in the case of cysts. This indicates rupture of the cyst with infection. Expectoration of hair and sebaceous material, known as trichoptysis, is the one pathognomonic symptom, although complaints by the patient of this occurrence have been received in the past with amused skepticism and incredulity. A circumscribed shadow in the anterior mediastinum is seen in the x-ray film, and the presence of teeth is pathognomonic. Thyromas and lymphoblastomas give shadows in the same position, but as these tumors are radiosensitive the shadow may decrease in

response to therapeutic radiation. Increasing pressure may lead to extrinsic stenosis of a bronchus, with occlusion, infection, pneumonitis, bronchiectasis, and abscess formation. For further details of teratoid tumors the reader is referred to the masterly paper by Rusby [41], which deals with all aspects of the subject.

Mediastinal Cysts

In this place, cysts other than those of the teratoid group will be considered. The dis-

tribution of bronchial, esophageal, gastric, and enteric cysts can be explained in this way. All these tumors occur in the posterior mediastinum, whereas the teratoid cysts and pericardial cysts are limited to the anterior mediastinum.

BRONCHIAL CYST

The bronchial or bronchogenic cyst is usually situated in the posterior part of the superior mediastinum, at the bifurcation of the

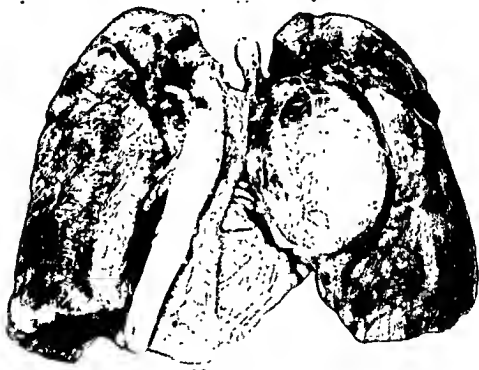


Fig. Introd. 2-14. Large bronchial cyst. (Courtesy Dr. S. A. Wallace.)

tribution is somewhat artificial, because both sets of cysts are developmental in origin. It is, however, of practical value, because these cysts never become malignant. Unlike the teratoid group, they do not contain dermal or epidermal structures. The cysts, depending on their structure, may be bronchial (bronchogenic), esophageal, gastric, or enteric (enterogenous). Pericardial cysts belong to a separate category.

The trachea and bronchi are formed from the primitive foregut. Laipply [27] suggests that a small bud or diverticulum of the gut may be pinched off, containing entoderm and mesoderm destined to become a part of the

trachea in particular, and attached to the carina or a large bronchus (Figure Introd. 2-14). It may, however, be found at any point along the line of the tracheobronchial tree in the lung, and even in the wall of the esophagus. The contents are mucoid or gelatinous. The lumen does not communicate with the bronchi. The distinctive feature is the lining of ciliated, pseudostratified, columnar epithelium. The wall of the cyst consists of fibrous tissue, smooth muscle, cartilage, mucous glands, and nerve bundles, i.e., the normal constituents of the bronchial wall (Figure Introd. 2-15).

Pressure symptoms, in particular cough,



Fig Introd. 2-15 Bronchial cyst ($\times 90$.) Microscopic picture of cyst shown in Figure Introd. 2-14

dysphagia, and cyanosis, generally develop in the first few months of life. There may be no symptoms, the cyst being found at autopsy.

ESOPHAGEAL CYST

This cyst is similar to the bronchial cyst, except that it is lined by squamous stratified epithelium and its wall resembles that of the esophagus

GASTRIC CYST

These cysts are found in the posterior mediastinum behind the trachea and esophagus, usually in infants and young children. The wall of the cyst resembles that of the stomach, and the contents are usually strongly acid (Figure Introd. 2-16). For this reason a chronic gastric ulcer may develop, which may erode the trachea and give rise to hemoptysis.

ENTERIC CYST

This rarest of the cysts is similar to the gastric cyst except that its wall presents the structure of the intestine.

PERICARDIAL CELOMIC CYST

The pericardial cavity is formed by the fusion of multiple disconnected lacunae. If one of these fails to fuse with the others, a cyst will result. It is regarded as being a great rarity, yet Lillie, McDonald, and Clagett [30] report twelve such removed surgically between 1941 and 1947. In contrast with the

other mediastinal cysts (exclusive of dermoids), this one occurs in the *anterior* mediastinum, generally at a cardiophrenic angle, twice as often on the right side, and is in contact with the pericardium, the anterior chest wall, and sometimes the diaphragm. The



Fig Introd. 2-16. Mediastinal gastric cyst showing structure of stomach wall ($\times 30$.)

lining is a single layer of flattened cells, and the contents are so clear and limpid that the cyst has been given the poetic name of "spring-water cyst." There are usually no symptoms, the cyst being discovered in routine x-ray examination or post-mortem, but occasionally there may be dyspnea or pain.

Miscellaneous Mediastinal Tumors

LIPOMA

This rare tumor is always benign and of slow growth, so that it may attain a very great size before producing symptoms. It is an anterior mediastinal tumor, which may remain

the case of teratoid cysts, neither of which are present in the case of lipoma.

CYSTIC LYMPHANGIOMA

This is perhaps the rarest of mediastinal cysts. It is a large, multilocular structure containing watery fluid and lined by endothelium. It probably arises from a portion of the anlage for lymphatic formation in the neck, which is drawn down by the descent of the pericardium.

THYMOMA

The thymus consists of: (1) epithelial cells which constitute the medulla, where they

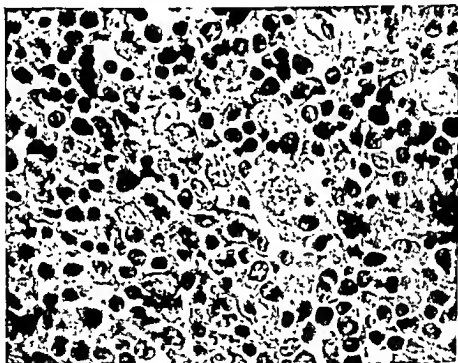


Fig. Introd. 2-17. Thymoma ($\times 510$)

intrathoracic or may grow up into the neck or out between the ribs. Removal is not difficult, but the patient may die soon after the operation if the tumor is large, for during its slow growth the heart and lungs have gradually become accustomed to strains and pressures that are suddenly released when the tumor is removed. It is with the teratoid tumors and cysts that the lipoma is likely to be confused. Its most characteristic radiologic feature is its translucency. An aspirating needle encounters resistance and reveals gelatinous material in

form Hassal's corpuscles, and the reticular cells of the cortex; (2) lymphoid cells which make up the greater part of the cortex (see Chap. 31).

Tumors of the thymus, situated in the anterior mediastinum, may be benign or malignant. The *benign* tumors tend to reproduce the various elements of the normal gland (Figure Introd. 2-17). They may attain a remarkable size, Andrus and Foot (1) reporting one weighing 2,335 Gm. which was successfully removed. The *malignant* thymoma may

consist principally of either of the two cellular components, lymphocytic or epithelial. It may, therefore, present a picture of lymphosarcoma or of epidermoid carcinoma, the latter being composed of innumerable thymic corpuscles in all stages of development and degeneration. A thymic tumor is sometimes present in myasthenia gravis. This has suggested removal of the thymus, whether or not a tumor is present, in the treatment of the condition, a procedure which has been attended with success in some cases.

LYMPH NODE TUMORS

Tumors of the lymph nodes, situated in the anterior mediastinum, form the largest group of mediastinal tumors. They may be primary or secondary. The primary tumors form the group of the malignant lymphoblastomas, of which the members are lymphosarcoma, reticulum-cell sarcoma, and Hodgkin's disease. Although general lymph node enlargement is the rule, it may be confined to the mediastinum. The marked radiosensitivity of the mass is of great value in distinguishing these neoplasms from other tumors of the anterior mediastinum. The secondary tumors are usually secondary to bronchogenic carcinoma, but the primary neoplasm may be in the abdomen, the esophagus, the breast, or the neck.

TUMORS OF THE CHEST WALL

Tumors of the chest wall may arise from the soft tissues or from the bone, either ribs or sternum. No reference need be made to the usual skin tumors.

Tumors of the Soft Parts

These may be benign or malignant. The chief representative of the former group is lipoma; of the latter, sarcoma. Lipoma is noteworthy chiefly because of the enormous size which it may attain. If it arises in the deeper part of the intercostal space, it may grow both outward and inward, assuming a dumbbell form like that of neuroma of the spinal nerves. Fibrosarcoma is the commonest of the malignant tumors. The microscopic appearance is often misleading, and the pathol-

ogist may be in doubt to such a degree that he may hesitate to make a diagnosis of sarcoma. The surgeon must not be misled by a report of doubtful or very low-grade malignancy. Unless his resection is wide and thorough, the tumor is likely to recur.

Tumors of Bone and Cartilage

The ribs and sternum are red marrow bones. This fact serves as a guide to the type of tumors which may be expected, for multiple myeloma and secondary carcinoma are tumors of red marrow.

Secondary carcinoma is the commonest tumor of the ribs and sternum. Mention may be made of secondary thyroid carcinoma, but with this exception these tumors do not demand further consideration here. Chondroma or chondrosarcoma is the chief primary tumor, usually in the ribs, occasionally in the sternum. Here, again, the microscopic distinction between the benign and malignant may be difficult or impossible, and the surgeon must govern himself accordingly, removing the periosteum, attached muscles, and underlying pleura. The tumor may enlarge very slowly for a number of years and then suddenly take on rapid growth; or growth may be rapid from the beginning. It seems justifiable to regard the first group as chondroma later becoming malignant, the second group as chondrosarcoma from the start. Rapid increase in size is on the whole a more reliable criterion of malignancy than is the microscopic picture. In the x-ray film the pure chondroma is invisible, it is seen only when calcification or ossification has occurred. In chondrosarcoma there may be extensive destruction of the bone.

Eosinophilic granuloma and fibrous dysplasia are benign lesions of the ribs which may readily be mistaken for malignant tumors. Giant-cell tumor, osteogenic sarcoma, and Ewing's tumor are rare. The ribs and sternum are common sites of multiple myeloma. Occasionally there may be a solitary myeloma of the rib that is amenable to surgical removal. For a detailed description of the various forms of tumors of the chest wall the reader is referred to Janes's excellent paper [22]

Physiologic Considerations in Surgery of the Chest

Herbert C. Maier

The morbidity and mortality attending radical operative removal of thoracic cancer are influenced by the surgeon's recognition of the associated physiologic alterations.

PULMONARY PHYSIOLOGY

The most important functions of the lungs are oxygenation of the blood and the removal of carbon dioxide. The respiratory process hinges on the two primary factors of an adequate movement of gases into and out of the lung, and proper perfusion of the pulmonary capillaries. These two processes are closely interrelated.

Adequate ventilation of the lungs requires a chest cage with sufficient mobility to permit (1) a satisfactory bellows mechanism for gas exchange with the outside atmosphere, (2) pulmonary tissue with reasonable elasticity, (3) the absence of obstruction in the tracheobronchial tree, (4) alveoli that are free of transudate or exudate, (5) the avoidance of interference with pulmonary ventilation by air and fluid in the pleural cavity, (6) a normal respiratory drive, and (7) a proper flow of blood through the pulmonary capillaries.

The bellows mechanism of the chest cage is produced by a complicated integration of movement of the chest wall and diaphragm. Impaired motion of one of these tends to be compensated for by augmented excursion of the other. Therefore, when the function of the chest cage is impaired, the diaphragmatic motion assumes much greater significance, and vice versa. If the movement of both chest wall and diaphragm is restricted at the same time, ventilatory insufficiency may result. In pulmonary emphysema the characteristic finding is a relatively immobile chest wall and a

low diaphragm with little respiratory motion. When the stability of the chest wall is impaired by extensive rib resection, as in the radical removal of a tumor of the thoracic wall, the normal ventilatory motion is altered. The decostalized portion of the chest wall no longer moves in the usual manner but has a paradoxical motion in relation to the phase of the respiratory cycle, with resultant reduction of respiratory function and abnormal mediastinal motion. Techniques that minimize such abnormal mobility of the chest cage must be employed.

Impairment of elasticity of the lung, as occurs in pulmonary emphysema, is the most important cause of respiratory insufficiency in the older age group with cancer of the lung. The operative risk and later disability of pneumonectomy are closely correlated with the degree of emphysema in the remaining lung. The respiratory insufficiency that may result from overdistention of an emphysematous lung after pulmonary resection must be borne in mind.

Moderate narrowing of the trachea or a primary bronchus may not interfere with air exchange before operation unless secondary bronchospasm or bronchial secretion is an additional factor. As bronchostenosis increases, obstructive emphysema and atelectasis may follow, with virtual loss of function. Obstructive emphysema may be overlooked on the usual roentgenogram but should be detected on fluoroscopic examination. Narrowing of the airway, which produces no symptoms preoperatively, may yet cause sufficient ventilatory interference to be a factor in the development of pulmonary edema during inhalation anesthesia with a closed system. A free airway without undue resistance to gas exchange

is a primary requisite of all thoracic surgery.

If the alveolar spaces contain transudate, blood, or exudate, air cannot have proper contact with the pulmonary capillaries.

The most frequent causes of pulmonary complications associated with thoracic operations are an inadequate airway, retained secretions or blood in the tracheobronchial tree, and overloading of the reduced pulmonary vascular bed from too much intravenous fluids and blood. Hypotension and hemorrhage increase the likelihood of pulmonary congestion.

Accumulations of air and fluid in the pleural cavity interfere with lung expansion. Not only is the lung partly collapsed, but associated impairment of chest wall and diaphragmatic motion may be present. When a patient is close to respiratory insufficiency, a small additional loss of respiratory function may be crucial.

A normal respiratory drive is a great safety factor. If the respiratory center is depressed by drugs, anesthetics, anoxemia, or marked carbon dioxide accumulation, ventilatory failure may be precipitated. Here, too, the vulnerability of the patient may be greatly influenced by the general nutritional, metabolic, and circulatory status.

A proper flow of blood through the capillaries of the lung is essential for the interchange of oxygen and carbon dioxide between the alveolar gases and blood. There is a remarkable correlation between pulmonary ventilation and pulmonary capillary flow. When the ventilatory function of a lung is diminished because of bronchial obstruction, by collapse of the lung from external factors, or by impaired motion of the thoracic cage, there is an early and rapid reduction in the pulmonary capillary flow through the corresponding portion of the lung with shunting of most of the right ventricular output to those parts of the lung which are well ventilated.

Normally the pulmonary vascular system is capable of a large increase in minute volume flow without an increase in pressure. If other portions of the pulmonary vascular bed are normal, considerable portions of lung may be excised or the capillary blood flow through large areas diminished without raising pul-

monary artery pressure. If there is diffuse narrowing of the pulmonary vessels, an increase in minute volume flow, as occurs during exercise, may result in an increase in the pulmonary artery pressure with resultant strain on the right ventricle. Resection of one lung results in a marked reduction in the pulmonary vascular bed, and adjustment to such an alteration will depend on the adequacy of the vascular bed in the remaining lung.

Most pulmonary tumors arise from the bronchial wall and tend to occlude the bronchus as the growth enlarges. Since this is usually a gradual process, the diminished ventilation of the involved segment, lobe, or lung is associated with a considerable reduction of blood flow through the pulmonary artery of the corresponding region. Therefore, most patients with a bronchogenic tumor, even if the main bronchus is obstructed, have no hypoxia prior to operation. The significant exceptions occur in the presence of associated diffuse pulmonary emphysema, obstruction to the airway of both lungs as by partial tracheal obstruction, an acute pneumonic process of recent occurrence, and impaired pulmonary circulation as in cor pulmonale or occasionally with diffuse carcinomatous metastases. Thus, hypoxia in a patient with a bronchogenic tumor unassociated with an acute pneumonia usually means that the opposite lung is not normal. Dyspnea and cyanosis require a most thorough study of respiratory and cardiac reserve.

ALTERATIONS DURING OPERATION

If the ventilation of the lung during a surgical procedure involving a widely open thorax is not sufficient to keep the arterial blood well oxygenated, the hypoxia produced thereby may cause early circulatory failure. An individual with good vital capacity withstands an open pneumothorax unassisted for a time, the patient with diminished pulmonary function may be unable to tolerate the accumulated physiologic maladjustment. The physiologic disturbances associated with such an open pneumothorax must be minimized. Pulmonary ventilation during operations requiring an open pneumothorax is controlled by the application of a slightly positive pressure within the tracheobronchial tree. This

also greatly diminishes the to-and-fro motion of the mediastinum with respiration. It must be recognized, however, that positive intrathoracic and intrabronchial pressure does have some deleterious effect on the circulation. The minimum amount of positive pressure necessary for adequate ventilation should be the goal. Positive pressure should be employed only during those portions of the operative procedure in which it is really required.

Respiratory acidosis is particularly apt to occur with shallow respiration during an intrapleural operation on an emphysematous patient, which may cause secondary cardiocirculatory effects during and immediately after operation. Ordinarily, the unanesthetized patient does not have any carbon dioxide retention if the respiratory function is adequate to maintain normal oxygenation of the arterial blood. Carbon dioxide retention with resultant acidosis may occur in association with the hypoxia of severe emphysema or of tracheobronchial obstruction; in such patients oxygen therapy, although lessening the hypoxia, may occasionally aggravate the respiratory acidosis because of the depression of respiration.

Some intrathoracic procedures may result in the simultaneous opening of both pleural cavities. This situation can be adequately managed. A small opening into the contralateral pleural space occurring during esophagectomy may occasionally lead to a large and serious pneumothorax because air becomes trapped in the opposite pleural cavity. The anesthetist can satisfactorily control the inflation and ventilation of both lungs provided that neither lung is compressed by trapped intrapleural air. Therefore, the surgeon must ascertain that a sucking type of pleural opening is not producing a progressively enlarging pneumothorax on the contralateral side. Immediate postoperative roentgen examination should be done in any case in which such a condition may exist. In the rare situation in which simultaneous drainage of both pleural cavities is necessary postoperatively, it is mandatory that suction drainage be employed, as ordinary water-seal drainage bilaterally may not permit adequate pulmonary function.

PNEUMONECTOMY

Pneumonectomy results in displacement of the mediastinum toward the side of operation with an associated overexpansion of the remaining lung. The anatomic and physiologic adjustment is more satisfactory following left pneumonectomy. Since the left lung is smaller than the right, there is less reduction in the vascular bed and also the heart makes a more satisfactory anatomic adjustment. For these reasons, circulatory and respiratory disability is likely to be greater after right pneumonectomy. The age of the patient and the status of the remaining lung, especially in regard to emphysema, are important factors. When pneumonectomy is performed in childhood, the ultimate respiratory function is better than when pulmonary resection is done in later life. The most important factor in the eventual respiratory function is the avoidance of such a degree of hyperinflation of the remaining lung that it becomes an inefficient ventilative organ. Considerable hyperinflation of a normal elastic lung may not interfere with pulmonary function, whereas a similar degree of overexpansion of a somewhat emphysematous lung may result in a respiratory insufficiency. Therefore, in some cases after pneumonectomy it is mandatory that mediastinal displacement be limited in order to lessen the overinflation of the remaining lung. Marked shift of the mediastinum after pneumonectomy can be prevented by a thoracoplastic collapse of the hemithorax from which the lung was removed.

In the older age group undergoing pneumonectomy for cancer, the frequent occurrence of emphysema demands a careful consideration of the undesirable features of mediastinal displacement and hyperinflation of the remaining lung. Otherwise, a considerable morbidity and mortality from right heart failure and pulmonary insufficiency may occur subsequently in patients who have a favorable prognosis from the standpoint of their neoplastic disease. In some cases respiratory function is so reduced that a more limited operation than pneumonectomy is dictated by physiologic considerations.

In the first few days after pneumonectomy, there is usually a slight drop in the arterial oxygen saturation. Oxygen therapy will cor-

rect this early postoperative hypoxia if the remaining lung is relatively normal. Although the patient may feel slightly short of breath after pneumonectomy, marked dyspnea in the postoperative period usually indicates serious abnormality in the remaining lung or cardio-circulatory failure.

Immediately after the completion of a pneumonectomy, it is most important that the intrapleural pressure be adjusted to a slightly negative level so that the mediastinal structures are not shifted, otherwise the patient may be left with a positive or highly negative intrapleural pressure with associated mediastinal displacement. The effects of such an abnormal physiologic status may not be clinically manifest at once. A positive intrapleural pressure may interfere with cardiac filling and precipitate circulatory failure, which is often erroneously attributed to a primary cardiac fault. If mediastinal displacement is avoided in the first few days after pneumonectomy, the incidence of cardiac arrhythmia and failure, pulmonary edema, and other respiratory complications will be reduced markedly. The gradual mediastinal shift that occurs in later weeks and months is compensated for by the patient.

LOBECTOMY

Following the resection of a lobe of one lung there is often a moderate drop in the arterial oxygen saturation for a period of a few days. This anoxia may be present even though the remaining lobe re-expands rapidly in the postoperative period. The hypoxia is due to a temporary imbalance between ventilation and circulation in the remaining lobe, caused by the temporary splinting of the side of the operation. If complications occur in the postoperative period following lobectomy, the duration of hypoxia may be longer. Oxygen therapy is desirable until the arterial saturation returns to normal. There is no

hypoxia after the early postoperative period unless other pulmonary disease is present.

The degree of change in lung volume and in residual air following lobectomy will vary depending on the extent of disease in the removed lobe and the condition of the remaining pulmonary tissue. In some cases in which the removed lobe is markedly diseased, there may be little alteration from the preoperative findings.

The effects of pulmonary resection on respiratory function vary with the amount of lung tissue removed. When a half or less of one lung is excised, the remaining part of that lung hyperinflates to occupy a volume somewhat less than that of an entire lung. After lobectomy, there is usually slight elevation of the diaphragm and perhaps slight mediastinal shift to lessen the size of the hemithorax. If the remaining lobe was normal, it may show a considerable increase in ventilation and a moderate increase in oxygen uptake after the lobectomy. If emphysema was already present in the lobe which remains on the side of the lobectomy, the resultant overdistention will cause a drop in the oxygen uptake in spite of an increased ventilation. An overdistended, emphysematous lung no longer is an efficient respiratory organ.

The most important physiologic considerations in the surgical treatment of thoracic cancer are related to disturbances in respiratory function. Many of the cardiocirculatory complications that are encountered are initiated or aggravated by interference with lung function and are not primarily due to heart disease, even though some cardiac changes may be present. When interference with ventilative motion and pulmonary circulation are kept to a minimum, morbidity and mortality are reduced. The same fundamental principles apply whether the operation is performed on the chest wall, lung, esophagus, or mediastinum.

also greatly diminishes the to-and-fro motion of the mediastinum with respiration. It must be recognized, however, that positive intrathoracic and intrabronchial pressure does have some deleterious effect on the circulation. The minimum amount of positive pressure necessary for adequate ventilation should be the goal. Positive pressure should be employed only during those portions of the operative procedure in which it is really required.

Respiratory acidosis is particularly apt to occur with shallow respiration during an intrapleural operation on an emphysematous patient, which may cause secondary cardiocirculatory effects during and immediately after operation. Ordinarily, the unanesthetized patient does not have any carbon dioxide retention. If the respiratory function is adequate to maintain normal oxygenation of the arterial blood, carbon dioxide retention with resultant acidosis may occur in association with the hypoxia of severe emphysema or of tracheobronchial obstruction; in such patients oxygen therapy, although lessening the hypoxia, may occasionally aggravate the respiratory acidosis because of the depression of respiration.

Some intrathoracic procedures may result in the simultaneous opening of both pleural cavities. This situation can be adequately managed. A small opening into the contralateral pleural space occurring during esophagectomy may occasionally lead to a large and serious pneumothorax because air becomes trapped in the opposite pleural cavity. The anesthetist can satisfactorily control the inflation and ventilation of both lungs provided that neither lung is compressed by trapped intrapleural air. Therefore, the surgeon must ascertain that a sucking type of pleural opening is not producing a progressively enlarging pneumothorax on the contralateral side. Immediate postoperative roentgen examination should be done in any case in which such a condition may exist. In the rare situation in which simultaneous drainage of both pleural cavities is necessary postoperatively, it is mandatory that suction drainage be employed, as ordinary water-seal drainage bilaterally may not permit adequate pulmonary function.

PNEUMONECTOMY

Pneumonectomy results in displacement of the mediastinum toward the side of operation with an associated overexpansion of the remaining lung. The anatomic and physiologic adjustment is more satisfactory following left pneumonectomy. Since the left lung is smaller than the right, there is less reduction in the vascular bed and also the heart makes a more satisfactory anatomic adjustment. For these reasons, circulatory and respiratory disability is likely to be greater after right pneumonectomy. The age of the patient and the status of the remaining lung, especially in regard to emphysema, are important factors. When pneumonectomy is performed in childhood, the ultimate respiratory function is better than when pulmonary resection is done in later life. The most important factor in the eventual respiratory function is the avoidance of such a degree of hyperinflation of the remaining lung that it becomes an inefficient ventilative organ. Considerable hyperinflation of a normal elastic lung may not interfere with pulmonary function, whereas a similar degree of overexpansion of a somewhat emphysematous lung may result in a respiratory insufficiency. Therefore, in some cases after pneumonectomy it is mandatory that mediastinal displacement be limited in order to lessen the overinflation of the remaining lung. Marked shift of the mediastinum after pneumonectomy can be prevented by a thoracoplastic collapse of the hemithorax from which the lung was removed.

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In the first few days after pneumonectomy, there is usually a slight drop in the arterial oxygen saturation. Oxygen therapy will cor-

ventilate his unaffected lung efficiently. If an elevated rest is used, respiratory movements may become impeded and the thoracic cage constricted to the extent that tamponade of the mediastinal structures may result. Particular attention must be given to the details of position when thoracic surgery is contemplated.

Although the risk involved in opening the pleural cavity has doubtless been exaggerated, the control of differential intrapulmonary pressure facilitates operation, reduces surgical shock, and decreases the incidence and severity of postoperative complications (see Chap. 14.)

Ventilation

It is imperative that the anesthetic regime provide an effective means to obviate inadequate ventilation in the presence of impending atelectasis. One widely used method for such provision is the technic that has become known as *controlled respiration*. Introduced some fifteen years ago, it is simply the use of continuous artificial respiration. Controlled respiration is practiced in man by depressing the respiratory center, either by increasing the anesthetic concentration of the drugs being used or by markedly reducing alveolar and blood carbon dioxide tensions through hyperventilation or a combination of the two, until automatic respiratory efforts are suspended. More recently, with the advent of curare and other drugs possessing a muscle-paralyzing action, apnea may be secured by giving them intravenously until respiratory muscles are no longer active. When the state of apnea is reached, rhythmic manual pressure on the breathing bag of the anesthetic appliance is carried out. A pressure in the range of 10 to 20 cm. H_2O is transmitted to the lungs at a rate of approximately 30 per minute to provide the inspiratory phase of respiration. Release of pressure permits a passive expiratory phase. If carbon dioxide is reduced, a period of apnea often follows prolonged controlled respirations and it is sometimes difficult for the anesthetist to provide immobility of the exposed lung or prevent it from bowing into the wound at each inspiratory phase of the maneuver.

Compensated respiration is another very

satisfactory method for preventing respiratory difficulties from altered pressures in the open chest. Spontaneous respirations are maintained but the inspiratory phase is reinforced or assisted by pressure on the breathing bag sufficient to avoid a state of pulmonary decompensation incident to pleurotomy.

The technical details are simple but very exacting. Pressure is applied rhythmically and intermittently with every inspiration of the patient. To avoid overventilation, the amount of pressure used is considerably less than when controlled respiration is in progress. Five to 10 cm. H_2O is regularly enough to satisfy respiratory requirements but insufficient to cause apnea. Accurate manometric determination of pressure used may be helpful but is not essential, since with little experience one learns the amount needed for the patient before him.

There are certain technicalities that must be rigidly adhered to if successful compensated respiration is to be obtained. The reinforcing inflations must be intermittently but continuously applied. A very transient period of interruption may permit the respirations to lose their established rhythm and it then becomes difficult at times to re-establish them. The pressure, when applied, should not be abrupt but must be a gentle, sliding one, causing the inspiratory phase to be somewhat more prolonged than the automatic effort would be of itself. The expiratory phase remains passive by releasing pressure from the breathing bag. The technic lends itself well to the convenience of the surgeon in that any degree of collapse of the lung may be obtained readily.

Recently, there have been introduced several mechanical respirators that can be adjusted to the desired volume exchange at a given rate and work automatically.

INTRATRACHEAL TECHNIQS

The primary requirement for positive intrapulmonary pressure is a patent airway that will transmit the pressure exerted in the upper respiratory tract to the lower. Pressure may be obtained with a continuous-flow apparatus having an expiratory valve with an adjustable spring that is arranged to blow off during expiration and remain closed during inspiration. The most satisfactory technic, however,

Anesthesia for the Surgical Treatment of Thoracic and Intrathoracic Neoplasms

Emery A. Rovenstine

Before the present century, the inability of anesthetists to avoid the desperate phenomena that had from ancient times been associated with collapse of the lung retarded progress in this field of surgery. Today the surgeon may manipulate within the pleural cavity with the security that he enjoys in intraperitoneal operations.

HISTORIC DEVELOPMENT

Previous to 1920 the apparatus and methods devised for intrathoracic surgery had scarcely more than a single objective, the prevention of pneumothorax. The earliest attempts utilized some form of intubation apparatus to supply air and the anesthetic agent directly to the lungs and maintain respirations artificially. As early as 1869, Trendelenburg had devised a tube surrounded by elastic rings, which made possible closed endotracheal anesthesia.*

There has been a careful comparative evaluation of the anesthetic methods, associated with a better understanding of such physiologic alterations as heat loss, water balance, acid-base equilibrium, the effects of slight respiratory obstruction, of slight oxygen deprivation, or of respiratory depression. Rowbotham and Magill, in England, reintroduced the large-bore, soft rubber catheter first used by Trendelenburg. Waters and Guedel added the inflatable cuff to insure airtight contact between the catheter and trachea. Anesthetic appliances were manufactured that permitted accurate regulation of intrapul-

monic pressure. New agents allowed adequate oxygen concentration with any degree of narcosis.

ANESTHETIC CONSIDERATIONS DURING INTRATHORACIC OPERATIONS

The surgical procedures employed in the treatment of thoracic and intrathoracic neoplasms present numerous and diverse anesthetic problems. If the procedure involves merely a superficial excision from the thoracic wall, satisfactory anesthesia may be simply and conveniently accomplished with gas-oxygen by any of the accepted techniques.

If the operation involves the entire thoracic wall, other techniques are required. The location of the tumor may demand a lateral approach with the patient upon his unaffected side or, in certain cases, in the face-down position. Maintaining an air-tight face mask in place in these awkward positions is difficult. The vascularity of the chest wall predisposes to considerable blood loss. Hemorrhage, frequently combined with severe trauma and embarrassment to pulmonary ventilation and circulation, contributes to circulatory depression that often terminates in shock.

The use of mechanical constricting devices to obtain better exposure for the surgeon, such as the elevating chest rest, usually embarrasses respiratory movements and may cause serious cardiocirculatory derangements. The lateral position often used offers the greatest possibility for elevated rests, sand-bag supports, and such other constricting devices to do the most harm. When the patient lies on his good side, while the affected side is uppermost, he may not be able to

*The references to anesthetic practices prevailing before 1930 may be found in Waters, R. M., E. A. Rovenstine, and A. F. Guedel: Endotracheal Anesthesia: Its Historical Development, *Anesth & Analg* 12:196, 1933.

ventilate his unaffected lung efficiently. If an elevated rest is used, respiratory movements may become impeded and the thoracic cage constricted to the extent that tamponade of the mediastinal structures may result. Particular attention must be given to the details of position when thoracic surgery is contemplated.

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employs complete rebreathing of anesthetic mixtures with the absorption of exhaled carbon dioxide and the continuous addition of oxygen sufficient for metabolic demands.

The endotracheal method has been universally adopted. There are no substantial ob-

with the handle and is intended to be inserted to a distance needed to engage the epiglottis and raise it forward to obtain a clear view (Figure 13-1). The other (MacIntosh) has a curved blade and is shorter (Figure 13-2). With it the tissues are contacted in front of

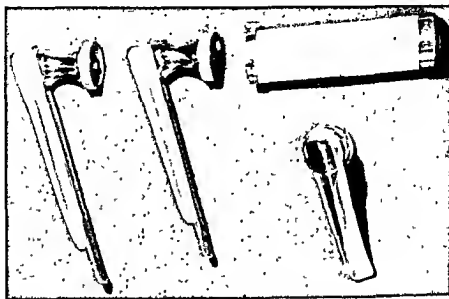


Fig 13-1. Laryngoscope with straight blades; various sizes.

jections to its use and no serious trauma follows, except where the technic is improperly applied. The contention that the difficulty of execution prevents its general acceptance is an accusation that anesthetists lack the skill to master a rather simple exercise. Every anesthetist should have the ability to insert a catheter in an unconscious patient.

ARMAMENTARIUM

The airways and other attachments used at present differ in almost every clinic and none has met all requirements. With the technics later described, most satisfactory results have been obtained with airways made from rubber or plastic tubing, size 24 to 32 F., soft enough to do no harm but with a thin, stable wall which is rigid enough to resist kinking and to support an inflated cuff. To provide airtight contact with the tracheal wall, an inflatable cuff is fitted near the tracheal end of the airway. To introduce the endotracheal airway by direct vision, a number of laryngoscopes are available. There are two popular models, differing somewhat in principle, in common use. One has a straight blade set at an angle

the epiglottis and, by tensing these, a clear view is also provided. The familiar soda lime canister and breathing bag used with the carbon dioxide absorption technic and a modern gas anesthesia appliance complete the equipment. The different connections, tube, inflatable cuff, etc., are illustrated separately and assembled in Figure 13-3.

In surgery of the thorax there is no indication for intubation by the nasal route and,

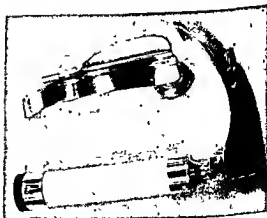


Fig 13-2. Laryngoscope with curved blade (MacIntosh).

with an inflatable cuff in place on a large airway, the oral direct-vision method is not only more easily performed but eliminates trauma to nasal mucous membranes.

ENDOBONCHIAL TECHNIQS

There have been a number of efforts to extend the endotracheal technics by inserting

off one lung. This prevents anything from one lung entering the other. The loss of anesthetic gases is avoided. Its use requires well-adjusted anesthesia

An important accessory to the equipment for successful anesthesia in thoracic and intrathoracic surgery is an efficient suction apparatus for the exclusive use of the anesthetist

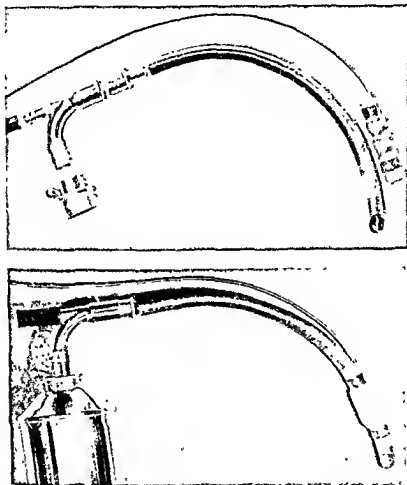


Fig 13-3. (Top) Soft-rubber endotracheal tube, inflatable cuff, and metal connections (Bottom) The same assembled as in use and attached to absorber for carbon dioxide.

the airway deeper into the lung so that its open end comes to rest in one of the primary bronchi. The need rarely is evident when operations are performed for the removal of neoplastic tissue from the thorax or its viscera

When the endobronchial technic is advised, the Carlen catheter (Figure 13-4) is the airway most often selected. This catheter is introduced so that its tip enters a bronchus, being held there by a small rubber piece which engages itself at the carina and thereby seals

Management of Secretions During and After Anesthesia

Another hazard during anesthesia for thoracic surgery is secretions, which may obstruct the airway and cause inadequate exchange with resulting asphyxia. Secretions aid the distribution of foreign material throughout the lung and predispose to such complications as pneumonitis, atelectasis, etc. Prophylaxis should be emphasized. Much may be done preoperatively by postural drainage.

This procedure should be carried out in the morning, to remove secretions accumulated during the night in preparation for operation in the early afternoon. The anesthetist's difficulties are increased if postural drainage is attempted immediately before anesthesia or after the preanesthetic medication is given. During anesthesia, postural drainage should be continued. It is always advisable to place

discredited. There is, of course, general agreement as to the value of an active cough reflex postoperatively. To favor its preservation and prevent stasis of secretions in the tracheo-bronchial tree, sedatives are minimized, changes in position utilized, and the cooperation of the patient enlisted. It may often be necessary to augment these measures by bronchoscopic aspiration.

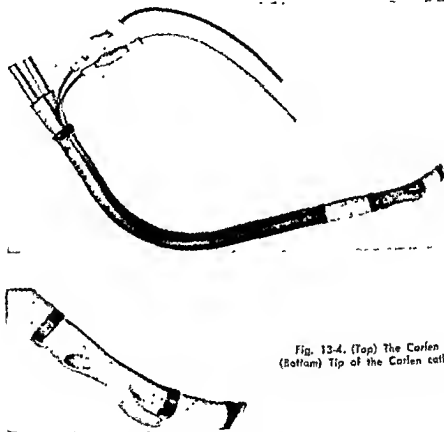


Fig. 13-4. (Top) The Carlen catheter complete (Bottom) Tip of the Carlen catheter.

the patient's lower respiratory tract at a level above the head. Such a position has the added advantage of protecting against cerebral air emboli. Some method for bronchial aspiration must be provided while intrapleural operations are in progress. Secretions will need to be removed frequently and emergencies will often arise, such as the sudden effusion of blood or the contents of a bronchitic cavity into the trachea, that may cause the patient to drown in his own secretions if aspiration is not available.

Coughing is the patient's mechanism for removing secretions. It has been suggested that this natural protection should be maintained during operation. The suggestion is

Control of Reflex Disturbances During Anesthesia

The complications of anesthesia during thoracic surgery, second only to those associated with inadequate ventilation, are described as reflexogenic, respiratory, or cardiocirculatory disturbances.

Disturbances involving the respiratory mechanisms include apnea and breathing irregular in both rate and amplitude. These are not considered as more than troublesome disturbances since they can be eliminated readily by properly controlled or compensated respirations.

The cardiocirculatory disturbances are of more consequence and their control is now of

major concern. The pulse rate may be altered frequently when manipulations are in progress about hilar structures. Slowing of the rate is not uncommon and even cardiac standstill has followed stimulation of the vagus nerve in the chest.

Much more common is the reflex alteration of the heart rhythm. These arrhythmias may be of any nature and of course include those of ventricular origin. When such disturbances occur, the peripheral circulation suffers, as evidenced by blood pressure changes. The keynote in the management of arrhythmias during anesthesia is proper prophylaxis and, in the event they occur, early efforts at effective therapy. Prophylactic measures include the early preparation of the patient, discussed elsewhere, and the avoidance of inadequate ventilation from mechanical sources such as constricting chest rests, position changes, and any of the many circumstances that may lead to anoxia.

"Bucking" is the commonly used term for a particularly disturbing reflexogenic phenomenon seen occasionally during intrathoracic surgery. It is actually an exaggerated coughing effort with the glottis held open by an endotracheal airway. The bucking movement is the result of convulsive spasms of the thoracic viscera and the muscles of the upper part of the body. This spasm reduces the size of the chest cavity and forces a burst of air through the glottis. If the glottis were not open, it would tend to expel any foreign material from the tracheobronchial tree. The primary muscles involved are the rectus abdominis, serratus anterior, the anterior spinal muscles, and, of lesser importance, the other muscles of respiration. When bucking occurs, the body is flexed in the lumbar region, the abdominal viscera are forced against the diaphragm, the head extends on the neck, and the shoulders jerk forward. It is accompanied by marked bronchiolar constriction, preventing efforts adequately to inflate the lungs. Bucking is less likely to occur if the upper respiratory mucosa has been anesthetized by the application of a local anesthetic agent previous to the placing of an endotracheal catheter. When it occurs, one needs to supply additional anesthetic agent and oxygen as rapidly as possible. The intravenous use of

curare will terminate an attack.

Hiccough, another muscular contraction—that of the diaphragm—may occur when the lungs are suddenly inflated. It can occur even though the patient is making no automatic respiratory movements. It is controlled by allowing the patient to accumulate carbon dioxide in the respiratory system.

Cough follows local irritation in the air passages. It can be initiated by irritation of afferent vagal fibers elsewhere. It is completed by closure of the glottis with a closed chest wall so that pressure in the airway may be increased by the contraction of the muscles involved in forced expiration. Cough cannot be tolerated during intrathoracic surgery. It will not occur if an endotracheal airway is in place and the chest open, since then pressure cannot be built up in the airway.

THE CHOICE OF ANESTHETIC AGENTS FOR THORACIC SURGERY

Nitrous oxide, ethylene, cyclopropane, or ether, among the inhalation agents, may be employed if given precisely and skillfully and if chosen when indicated.

An ideal agent should provide an easy induction and even maintenance of narcosis. It should have no toxic effects upon tissues during or after its use. Recovery from the action of the agent should follow rapidly the discontinuance of its administration. It should allow adequate oxygenation even in the presence of decreased minute volume respirations. It should not increase the secretions nor prove irritating to the respiratory passages. Finally, it should not greatly increase respiratory effort and should lend itself to the convenient application of the chosen technic. The selection of the agent most nearly to fulfill these requirements will not depend entirely upon the pharmacologic action of the drug. The technic of administration, the surgical procedure, and, more particularly, the condition of the patient will influence its choice.

Ether may be irritating to respiratory membranes, stimulate respiration, and increase secretions. Recovery is often unpleasant and slow, and the aftereffects undesirable. Its use for thoracic operations should be confined to the addition of amounts to an anesthetic mixture composed chiefly of the less potent gases,

to permit increased oxygen tensions.

Nitrous oxide possesses the qualifications for an ideal agent with the exception of potency. When using nitrous oxide with the whole or part of one lung out of action, and if preanesthetic sedation is minimized so as not greatly to impair reflexes, it often is impossible to supply a percentage of oxygen necessary to prevent anoxemia and still have a sufficient saturation in the blood to maintain surgical anesthesia.

Ethylene is considered a more potent agent than nitrous oxide and surgical anesthesia may be obtained with a higher oxygen dilution. However, with ethylene the same complication, namely, oxygen deprivation, is often encountered. Neither of these gases reduces reflex irritability sufficiently to permit easy tracheal catheterization.

Cyclopropane is a gaseous agent permitting any degree of narcosis with low concentrations. Regularly, more than 50 per cent of the anesthetic mixture is oxygen. The gas does not stimulate respiration. It provides induction and recovery that are more pleasant and as rapid as with other gaseous agents. It has little effect upon either diseased or normal respiratory tissues. Stimulation of secretions is minimal. Owing to the potency of cyclopropane, placing an endotracheal catheter is simplified. Controlled or compensated respirations may be maintained with this agent more conveniently than with any other. Cyclopropane, like ether and ethylene, is explosive and may not be used with safety if cautery is employed by the surgeon. The danger of explosions has caused many surgical clinics to avoid its use. A more general criticism of cyclopropane is directed toward the somewhat higher incidence of circulatory disturbances that may be noted when it is used in comparison, for example, with ether, intravenous barbiturates, or the less potent gases. In the experimental animal, increased cardiac irritability from cyclopropane has been demonstrated. Studies with human subjects have not disproved these laboratory conclusions. This criticism is more logical, particularly when manipulations are progressing that involve thoracic viscera. Avoidance of cyclopropane, however, does not eliminate such untoward reflex effects. The solution is probably in view

with the efforts in their prevention and prompt treatment with other drugs. Increased bleeding during cyclopropane anesthesia has been suggested from clinical observation, although conclusive evidence is lacking. Coagulation and bleeding times are decreased. The greatest disadvantage with cyclopropane is the difficulty surrounding its safe administration. The technic is exacting and a serious overdose is easily given. Although cyclopropane undoubtedly possesses advantages for some patients during thoracic surgery, these do not indicate its use by the anesthetist who regularly employs other agents and only chooses cyclopropane for an occasional thoracic case he may anesthetize.

With the advent of the more potent *barbituric acid derivatives*, permitting intravenous administration to secure the rapid onset of unconsciousness, these drugs have become increasingly popular for the induction of anesthesia and as an adjunct to its maintenance. The experiences of anesthetists during wartime added materially to the popularity.

Pentothal sodium is presently the most popular of the intravenous drugs available. When given in concentrations of 2 to 3 per cent, the patient is practically assured of a pleasant, rapid loss of consciousness, and the anesthetist, rarely confronted with an excitement stage, is free to carry out his various activities. If the drug is continued by intravenous drip of more dilute solutions (0.1 to 0.3 per cent), unconsciousness is easily maintained. Pentothal is desirable not only for rapid induction but for the pleasant rapid recovery that usually follows and the minimal incidence of postanesthetic nausea. The drug, however, should not be considered as a true anesthetic agent in the sense that ether or cyclopropane is, and its use as a total anesthetic agent is neither necessary nor advisable during thoracic surgery. Its analgesic properties are not proportional to its depressant effect, particularly on respiration, and another anesthetic drug should complement it. Nitrous oxide is less toxic than the more potent inhalation agents but its use invites anoxemia. Cyclopropane or ether is more desirable and may be required in small amounts only. With them, any amount of oxygen dilution is available. Pentothal sodium has been found to have a

parasympathomimetic effect and for this reason may sensitize the mechanisms of laryngospasm, bronchospasm, and coughing. This is of considerable importance when thoracic surgery is contemplated. However, when doses are small and not given rapidly, serious trouble from these reflexes is rare. A more considered disadvantage of Pentothal is that of its elimination. The drug is not rapidly destroyed or eliminated from tissues, but is stored readily in most tissues, particularly the fats. The rate of elimination is some 15 per cent per hour. The total dose of the drug given for any one operative procedure is, therefore, of most importance. To prevent accumulation and prolonged postanesthetic depression, doses of 2.0 Gm. should rarely, if ever, be exceeded.

When an explosive mixture must be avoided, an intravenous barbiturate for induction followed by nitrous oxide and oxygen is the procedure of choice. In many clinics this represents the procedure utilized for the greater part of all inhalation anesthetics.

When drugs such as Pentothal are used for induction, 2 or 3 cc. doses of 2.5 per cent are given every half to one minute until the patient is asleep. The induction is rapid and pleasant. When it is to be administered throughout the operation, a weaker solution is employed. During long surgical procedures it has been common practice to complement thiopental nitrous oxide oxygen anesthesia with Meperidine (10 to 15 mg.) or an opiate intravenously, to avoid giving large amounts of the barbiturate.

Curare and similar drugs that produce muscle relaxation have a limited value during thoracic surgery. They have no anesthetic effect, but a small dose sufficient to facilitate endotracheal intubation is often used immediately after the patient is unconscious and at the time the airway is to be placed. Muscles of the face and neck will not then impede the use of the laryngoscope.

MAINTENANCE OF ANESTHESIA

Anesthesia for thoracic and intrathoracic surgery may best be maintained by the carbon dioxide absorption technic. It is dosimetric and permits constant control of the anesthetic concentration. A warm, moist atmosphere is

in contact with the lung at all times. Carbon dioxide and oxygen exchange are directly controlled by the anesthetist and the dangers of anoxia or acarbica are diminished. The normal respiratory tract is enlarged by placing over the mouth and nose an airtight face mask, supplying an absorbing unit containing an alkali, and adding a rebreathing bag. The intratracheal airway made airtight within the trachea by an inflated cuff may replace the face mask. Within this enlarged respiratory system, without an exhaling valve, an anesthetic concentration that produces the required degree of narcosis is continually rebreathed. With anesthetic equilibrium established, oxygen only is added and that at a measured rate of flow just sufficient to supply the metabolic requirements of the patient. Adjustments during the operation may be necessary and more of the anesthetized agent or oxygen may be added as needed. The chemical reaction between the alkali and carbon dioxide exhaled will generate heat and maintain a warmed respired atmosphere. The water vapor in the patient's exhalations will be retained in the system and completely humidify the anesthetic mixture. No obnoxious or toxic gases or vapors will contaminate the operating room. The carbon dioxide content of the inspired atmosphere will be reduced to that normally respired in air, since all the exhaled gases are depleted of carbon dioxide in the absorber. It is well to remember that, with an airway in the trachea attached directly to a carbon dioxide absorption unit, the dead space for accumulating carbon dioxide, which is usually represented by the upper air passages and the anesthetic face mask, is reduced. A large-bore connection between the tracheal catheter and the absorber may be needed to supply additional dead space. The length of the endotracheal catheter should be as short as possible because the resistance to respirations is proportional to the length of the tube. This technic offers a means of directly controlling respirations. Breathing may be stimulated by shunting the respirations around or by removing the absorber from the system, thus allowing carbon dioxide to accumulate. Decreased respiratory movements amounting to apnea may also be obtained. Such decrease of respirations is accomplished by increasing

the anesthetic tension in the system and then by manual compression of the breathing bag, synchronous with inspiration, increasing the volume interchange of respired gases through the absorber.

The control of intrapulmonary pressure while employing the carbon dioxide absorp-

tion technic is readily maintained by partially distending the rebreathing bag and manipulating it by manual pressure. The pressure may be gauged with manometer or, more conveniently, by observation of the exposed lung.

Preoperative and Postoperative Management in the Treatment of Neoplasms of the Chest

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and
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Many aspects of preoperative and postoperative care in the surgical treatment of neoplasms of the chest are similar to those of other surgical conditions elsewhere. In addition, surgical intervention in this location poses many specific problems. This discussion will be concerned specifically with the problems related to the thorax.

PREOPERATIVE CARE

The Operative Risk

The preoperative management of patients with neoplasms of the chest consists of two phases. The first involves separation of those patients who are unable to withstand the necessary surgical procedure. The second phase involves bringing those patients suitable for operation into the best possible condition in the time allowable before the operation.

There are but two pathologic conditions, aside from extent of the tumor, which would contraindicate removal of a malignant neoplasm. First, diseases so severe as to give a prognosis of death earlier than the inevitable fatality from the untreated cancer, secondly, pathologic states so incapacitating that the extensive surgical operation necessary for their removal would have a fatal result. Examples of such conditions are: congestive heart failure that does not respond to treatment and extensive bilateral active pulmonary tuberculosis or pulmonary insufficiency of such degree that the patient is dyspneic at rest. Severe hypertension, marked arteri-

osclerosis, auricular fibrillation, or a history of one or more episodes of coronary occlusion, mild degrees of emphysema and quiescent pulmonary tuberculosis, while increasing the risk, do not contraindicate surgical removal of apparently operable intrathoracic malignant neoplasms. In dealing with benign neoplasms of the thorax that are not producing symptoms and do not constitute a threat to life, the contraindications are, of course, more numerous, because one is not justified in taking the same risks to remove benign growths as when one is dealing with malignant tumors. Thus, serious operative risks may be justifiably assumed when the patient has an apparently operable malignant neoplasm. With proper preoperative management patients with rather severe concomitant diseases may withstand the hazards of operative intervention.

A final point should be emphasized. The decision as to whether or not a particular patient constitutes a justifiable operative risk must always rest with the surgeon and not with the medical consultant or the family physician. The surgeon is always as well or better qualified to make this judgment because of his greater experience in observing patients before and after operations.

Preparation of the Patient for Operation

It is rarely necessary to postpone operation more than a week or ten days in order to improve a patient's condition [4]. Abnormalities of function should be detected and, if

the anesthetic tension in the system and then by manual compression of the breathing bag, synchronous with inspiration, increasing the volume interchange of respired gases through the absorber.

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be necessary preoperatively. Some of these patients manifest some difficulty in urination on the first day or two after operation. These respond well to catheter drainage; surprisingly few have required transurethral resection.

NUTRITION

Most patients with malignant thoracic neoplasms have lost weight. With cancer of either the lung or the esophagus, no time should be wasted in attempts to have the patient gain weight before operation. An adequate calorie intake should be supplied to these patients while they are being prepared for operation (Vol. I, Chap. 9).

BLOOD VOLUME

Anemia should be corrected preoperatively by blood transfusion. Because operation necessarily disturbs the normal processes of ventilation, it is particularly important not to add to this disturbance a deficiency in the mass of the hemoglobin that is essential to the oxygen transport. Although anemia, as shown by the concentrations of hemoglobin or of the erythrocytes, is not common in these patients, a reduced blood volume and hence a reduced mass of circulating hemoglobin is the usual finding in patients with esophageal cancer, especially those who have lost weight [1]. In an average-sized adult male who has lost thirty to forty pounds there will usually be a blood volume deficiency of 1,000 to 1,500 ml., which must be corrected preoperatively by transfusion. In general, the blood volume deficiency will parallel the weight loss. A blood volume determination is the only accurate measure. A diminished blood volume should be suspected when a transfusion fails to raise the hemoglobin of a patient who is not bleeding.

PSYCHOLOGIC PREPARATION FOR OPERATION

The patient's fear and anxiety can be greatly alleviated preoperatively if the surgeon will explain a few facts. The nature of the problem and the treatment necessary should be described in general terms. The possible favorable prognosis should be mentioned. The patient should be told that it will be necessary for him to remain in the hospital only ten or

twelve days after the operation and that he may get out of bed the day following operation.

The day before the operation, it is advisable to tell the patient that when he awakens from the anesthetic he will be in an oxygen tent until the following day or longer, and that this is routine procedure. He should be told that it is important for him to cough effectively after operation and that his operative wound will be painful during this active coughing. It is wise to ask him to cough a few times during this session. He should be instructed to dorsiflex and extend his feet and toes while in bed postoperatively, in order to increase the blood circulation in his calf muscles. Simple explanations of this sort before the operation are not time-consuming and are valuable in obtaining co-operation and achieving a smooth convalescence.

POSTOPERATIVE CARE

The postoperative care starts in the operating room at the conclusion of the operation. In the following discussion it is assumed that the operative care has been adequate, that an intratracheal tube has been employed, that the airway has been kept free of secretions, and that the blood lost during the course of the operation has been accurately replaced as it was lost [10]. It is further assumed that ventilation during the operation has been adequate so that respiratory acidosis has not occurred [9], and that an excessive amount of the anesthetic agent has not been administered.

THE DRESSING

The most comfortable dressing for thoracic wounds consists of a single layer of very fine mesh gauze bandage laid directly over the skin incision. This in turn is covered by a quantity of fluffed gauze, held in place by strips of elastic adhesive plaster extending three inches beyond the mid-line posteriorly and anteriorly, applied with only slight tension. The ends of the strips of elastic adhesive should be kept from curling by covering them with vertical strips of ordinary adhesive plaster. If this dressing has been properly applied it need not be removed until the skin stitches are removed on the seventh or eighth

possible, corrected. Obviously, patients with neoplasms of different intrathoracic organs will present problems peculiar to those lesions. This phase of preoperative care can best be considered under the various systems (for detailed discussion of this subject, see Vol. I, Chap. 10).

CARDIAC FUNCTION

The most valuable aid in the detection of impaired cardiorespiratory function is the history, or the demonstration, of the patient's capacity for effort. The ability to climb stairs at a normal rate without becoming short of breath is of more significance with regard to the functional capacity of the cardiorespiratory system than multiple laboratory tests. Past episodes of cardiac decompensation, cardiac arrhythmia, or episodes of coronary occlusion must be evaluated. A preoperative electrocardiogram is not necessarily a routine procedure in young people. On the other hand, even with no suggestion of heart disease a preoperative electrocardiogram is valuable in older patients for comparison with one made postoperatively. Preoperative postero-anterior and lateral roentgenograms of the chest should be made routinely. These x-ray films should be recent (within a week) in order to avoid missing a recent intrathoracic change. Comparison of the size and position of the heart preoperatively and postoperatively is helpful.

If the patient is decompensated, he is digitalized but there is no indication for prophylactic preoperative digitalization. Rapid digitalization of patients is now possible if it should become necessary in the postoperative period. Quinidine sulfate has occasionally been used preoperatively in elderly patients in the hope of avoiding auricular fibrillation during the postoperative period.

PULMONARY FUNCTION

In the majority of cases a clinical observation of the patient's capacity for effort is a satisfactory means of evaluating the respiratory reserve of patients with intrathoracic neoplasms. Only in those patients with a border-line respiratory reserve are pulmonary function studies routinely used. Some patients whose function is decreased by some

component of bronchospasm show marked improvement with the use of intermittent positive pressure breathing combined with a bronchodilator. For maximum benefit this treatment should be continued for from seven to ten days. This makes it possible to operate on otherwise inoperable cases. In these patients this treatment should be continued in the early postoperative period.

The determination of the vital capacity is a simple test. The maximum breathing capacity is slightly more difficult to determine with accuracy. Both the vital capacity and the maximum breathing capacity require the co-operation of the patient and so are not completely objective tests of pulmonary function. Pulmonary function studies of a more elaborate kind are still in the process of being evaluated with regard to their prognostic significance. At present they are important research tools, but for practical purposes are less valuable than determinations of the patient's capacity for effort without dyspnea. The results of functional studies must be considered in the light of the patient's primary disease. Impaired pulmonary function may be the result of destruction by the tumor of functioning pulmonary parenchyma, or the blocking of a large bronchus by the tumor. If an entire lung is thus rendered functionless, little or no further impairment of pulmonary function will result from the surgical removal of the involved lung. When a pulmonary neoplasm obstructs a bronchus, the patient may be febrile because of retained secretions and infection distal to the tumor. It is good practice in such cases to administer antibiotics prior to operation. If fever persists, operation should not be postponed, as only the removal of the affected lobe or lung will eliminate its cause.

RENAL FUNCTION AND THE URINARY TRACT

Cancer of the lung is nine times as frequent in men as in women, and occurs in the older age groups. In this group, benign prostatic hypertrophy is more common. Evidence of hypertrophy or a history suggestive of obstruction should be evaluated. If the patient is not retaining nitrogenous products, operation need not be deferred. If there is retention, catheter drainage can usually correct it. This has rarely

leave the patient with a slightly negative pressure. A more common disturbance of the intrapleural air pressure on the side from which the lung was removed is a high negative pressure resulting from the passage of air from the pleural cavity through the operative wound, or through the opened parietal mediastinal pleura, into the subcutaneous tissues, where it is trapped and does not re-enter the pleural cavity. This passage of air occurs during the momentary increase in intrapleural pressure with the act of coughing. The high negative pressure produces overdilatation of the remaining lung and may cause severe dyspnea. The condition is accurately diagnosed by measuring the pressure with a water manometer, and easily relieved by permitting atmospheric air to enter the pleural cavity through the needle until only a slight negative pressure is present.

MANAGEMENT OF SUBCUTANEOUS EMPHYSEMA

Even though the thoracic wound is airtight, subcutaneous emphysema may result from passage of air into the neck along anatomic planes, particularly following a radical pneumonectomy with extensive dissection of the lymph nodes along the trachea. In such radical pneumonectomies, it is almost impossible to obtain an airtight closure of the mediastinal parietal pleura. Subcutaneous emphysema from this source as well as from the operative wound usually reaches its peak during the first twelve to thirty-six hours, and thereafter is gradually reabsorbed. This subcutaneous emphysema, while producing mild discomfort, has no particular treatment and is rarely marked. If it becomes so extensive that the patient cannot see because of swollen eyelids, symptomatic relief can be provided quickly by a small skin incision in the lower neck or chest. The air can then be gently stroked out of the subcutaneous tissues of the face toward the small incision, where it escapes.

In instances of marked emphysema, it is important to find and correct the cause. Emphysema is indicative of a continuous air leak into the pleural cavity. After a pneumonectomy, such an air leak can occur from the bronchial stump only, an extremely rare oc-

currence in the early postoperative days. Following a lobectomy, the air leak may occur either from the bronchial stump or from the raw surface of the remaining lobe or lobes. Finally, if no pulmonary tissue is resected, a continuous air leak can only come from an accidental tear made in the lung on the side operated upon. Such inadvertent injuries to the lung may occur when there are extensive intrapleural adhesions. This complication requires immediate and continuous aspiration of the air. In an emergency this is accomplished by leaving the aspirating needle in place anteriorly, supporting it by a cork, and attaching the needle to a tube with the end of the tube under water. The air will then bubble out through the water and avoid the development of either a tension pneumothorax or further increase in the subcutaneous emphysema. As soon as practical, the needle should be replaced by a closed intercostal tube drainage connected with a source of constant negative pressure of 8 cm. water. Further care of this complication of a bronchopleural fistula will be considered under the heading of Complications.

CONTROL OF POSTOPERATIVE PAIN

The amount of postoperative pain varies greatly. Johnson has recommended dividing several intercostal nerves above and below the incision [7]. We have not adopted this practice generally because it tends to increase the area of altered sensation in the skin around the anterior end of the incision. With an anterolateral intercostal incision, it is good practice to use absorbable material for the pericostal sutures above and below the incised interspace. Similarly, with sternum-splitting incisions, sutures encircling the sternum to hold the two halves together should preferably be of the absorbable type. The use of silk or cotton in these two situations apparently results in greater and more prolonged postoperative discomfort than when catgut is used.

Morphine or Demerol should be given in amounts sufficient to alleviate the pain of coughing. A comfortable patient will cough more effectively. Thirty to forty-five minutes after every dose of morphine the patient should be made to sit up and cough. For the average-sized adult, 10 or 15 mg. of morphine

postoperative day. The advantage of the elastic adhesive plaster over the ordinary variety is that with coughing, breathing, and other movements that involve the thorax the elastic adhesive yields slightly yet maintains its original position.

ANTIBIOTICS

We have abandoned the routine use of prophylactic antibiotic therapy. If the patient is febrile preoperatively, antibiotic drugs should be employed before operation. In the postoperative period antibiotics are used only after the demonstration of frank pus or contamination during operation. The specific antibiotics used depend upon sensitivity studies.

DRAINAGE OF THE PLEURAL CAVITY

Following lobectomy, a catheter is inserted in a stab wound to drain the most dependent portion of the remaining pleural space. For the lower lobes, this is usually a low interspace in the axilla. Occasionally an additional catheter is inserted anteriorly and superiorly to take care of any leak of air. These are joined together by a Y-tube, and then connected with the same drainage system. Any type of catheter or drainage tube may be employed. A large-bore latex rubber tube with several side openings near the open end of the tube that lies in the pleural cavity has proved satisfactory.

The drainage tube system should provide for the escape of fluid and air and prevent their accumulation in the pleural space. The latter requirement is the essential difference between drainage of the pleural cavity and drainage of other parts of the body. The simplest drainage system consists in placing the end of the rubber tube connected with the catheter just under the surface of water in an open bottle or jar, which is placed below the level of the patient's thorax. Fluid and air can escape into the water, but air cannot enter the chest. With the negative pressure of inspiration, fluid will merely rise up in the tube. The objection to such a simple system is that the fluid that is drained from the chest is mixed with the water. Therefore, every drainage system should have a trap bottle inserted in the line to collect the fluid draining

from the chest. If a large air leak is present, it may be necessary to add a constant source of negative pressure. The negative pressure is kept below 8 or 10 cm. of water by a simple water valve. The character and the quantity of the fluid drained from the pleural cavity should be noted and recorded every 24 hours. When proper tube drainage is employed, subcutaneous emphysema rarely occurs because no positive pressure develops during coughing when air can escape through the tube.

CONTROL OF INTRAPLEURAL PRESSURE

Drainage of the pleural cavity is unnecessary after many intrathoracic operations (e.g., pneumonectomy). In these cases, following an airtight closure of the chest, the patient is placed in the supine position on the operating table and a needle is inserted in the second or third interspace in the mid-clavicular line anteriorly. The needle is connected with a water manometer and the pressure adjusted until it fluctuates with respiration at slightly negative values, 0 to -8 cm. of water. Too great a negative pressure will tend to increase the serosanguineous effusion that always occurs in the pleural cavity from which the lung is removed. On the other hand, a positive pressure will produce a shift of the mediastinum to the opposite side with resultant impairment of the function of the remaining lung.

During the first two or three postoperative days, marked changes may occur in the air pressure within the pleural cavity from which the lung has been removed. If, for example, a considerable effusion of serosanguineous fluid occurs in the pleural cavity and if the thoracic wound is airtight, the remaining air will be compressed, the mediastinum will shift to the opposite side, and there may be marked dyspnea. The condition can easily be recognized by inserting a needle in the upper anterior chest. A positive pressure at this juncture can be treated by further removal of air, but is perhaps best dealt with by inserting a needle in the eighth interspace posteriorly in the scapular line, withdrawing as much of the serosanguineous fluid as can be obtained, and at the same time replacing the fluid with a somewhat smaller volume of air so as to

tree. The procedure is simple. A catheter of a size that can be passed easily through the nostril is passed back to the pharynx. The patient is asked to protrude his tongue, which is grasped with gauze with one hand. Then while the patient makes a deep inspiration, the catheter is rapidly advanced into the trachea with the other hand. That the tip of the catheter is in the trachea can easily be ascertained by noting the passage of air out of the catheter on expiration. Intermittent suction is then applied to the catheter while it is gently turned and moved up and down in the trachea. If the secretions are particularly viscid, one or two milliliters of sterile physiologic saline may be cautiously introduced, followed by renewed aspiration. When no more secretions can be obtained, the catheter is withdrawn. The tracheobronchial tree is cleared of secretions not only by the aspiration but also by the coughing stimulated by the procedure. Aspiration should be done whenever coarse rales are present that cannot be cleared by the patient's coughing. Again, when the patient is febrile from no obvious cause, and when the cough is not productive, nasotracheal aspiration will often result in the removal of thick secretions, followed by decline in the fever. All members of the resident staff should be skilled in the technic of nasotracheal aspirations.

The routine use of nasotracheal catheter aspiration has reduced the need for bronchoscopic aspiration. Only in rare instances is it necessary to perform a tracheotomy in order to have easy access to the trachea. However, if a patient is unable to keep himself clear of secretions by coughing, and when there is difficulty in passing a catheter through the nose into the trachea, there should be no hesitation in performing a tracheotomy.

ADMINISTRATION OF BLOOD AND PLASMA

Blood lost during the operation should be measured and quantitatively replaced. There is a further loss postoperatively from injured tissue into the pleural space, where fluid accumulates or is drained externally. Generally, the serosanguineous fluid has a hematocrit of between 5 and 20 per cent cells, indicating a larger loss of plasma than of whole blood.

The greatest loss of this serosanguineous fluid occurs in the first twelve hours, with diminishing amounts lost thereafter. A significant increase in the hematocrit of arterial blood on the morning following a major intrathoracic operation has been noted unless plasma or a plasma substitute was given following operation. Because of the expense and the danger of serum hepatitis, we prefer to use a plasma substitute rather than human plasma. A unit of this is regularly given slowly through the night of operation. A hematocrit determination is routinely performed the morning after operation. If this is high, more plasma substitute is indicated; if it is low, more blood is needed. It is especially important to avoid administration of excessive amounts of blood or plasma in patients with impaired cardiac function.

POSTOPERATIVE ROENTGENOGRAM

A posteroanterior roentgenogram of the chest in the erect position should be obtained routinely on the first postoperative day. This can be done at the bedside, without disturbing the patient, by using a portable x-ray machine. The position of the mediastinal structures and the condition of the pulmonary parenchyma can be seen on such a film. After a lobectomy, the degree of expansion of the remaining lobe or lobes is apparent. After operations in which closed tube drainage is not employed, the film is helpful in indicating the extent of the pleural effusion. The film will indicate the position of the Levin tube in esophagectomies and esophagogastric resections. It will show the position of the stomach in the chest and whether or not it is distended with fluid or air. Subsequent x-rays may be required.

THE POSTOPERATIVE REGULATION OF WATER AND ELECTROLYTES

See also Volume I, Chapter 9.

We have shown that following major intrathoracic operations, the urinary excretion of sodium remains low for the first five postoperative days; excretion of potassium during the same period continues at its preoperative level [1]. The urinary excretion of chloride in general parallels the change in the sodium. It appears, therefore, that the administration

may be given every fourth hour when necessary during the first twenty-four or forty-eight hours. Patients rarely require narcotics for chest pain beyond forty-eight hours.

POSTOPERATIVE ADMINISTRATION OF OXYGEN

During the transportation of the patient from the operating room to the bed, it is well to administer oxygen by means of a face mask and a simple demand valve. In the patient's room we prefer the use of an oxygen tent, despite the fact that it is difficult to obtain high concentrations of oxygen, for patients are more comfortable without the presence of a nasal catheter. Furthermore, during the summer heat, the cool atmosphere in the oxygen tent adds considerably to the comfort of the patient. Increasing the humidity in oxygen tents from the usual level of 30 to 40 per cent up to 80 or 90 per cent seems to ease coughing up tracheobronchial secretions.

The oxygen tent is used continuously for the first twelve hours or so and thereafter intermittently. There is no set time that oxygen should be employed postoperatively. If there is no increase in the pulse or respiratory rate and no cyanosis without oxygen, it may be safely discontinued. Studies of the oxygen saturation of the arterial blood during operation and two hours postoperatively when the patient is in bed in an oxygen tent have shown a decrease in the saturation from a high normal level to an average of 89 per cent. Without the use of oxygen, the arterial saturation would probably have been even lower. Cyanosis should not be regarded simply as an indication for higher concentrations of oxygen. It indicates some disturbance in the intrathoracic pressure relationships, or, even more frequently, some obstruction in the tracheobronchial tree by secretions, mucus, blood, or pus.

POSITION IN BED AND MUSCLE FUNCTION

Postoperatively, the patient is placed in bed in the supine position with the bed level while the blood pressure and pulse rate are taken and breath sounds noted. After the patient recovers from his anaesthesia, the head of the

bed is gradually elevated until the patient is in a semirecumbent position. In this position he is able to breathe with less effort because the weight of the abdominal contents does not press upon the diaphragm. It is also the position in which cough is most effective. The patient is required and encouraged to flex and extend his ankles and toes. There should be no fixed practice about position, but the patient should be allowed to assume the position which is most comfortable. He is also encouraged to move as much as possible in bed. The semirecumbent position should be varied by making the bed level at intervals, if this does not make the patient dyspnoeic. When the bed is level, he should lie first on one side and then on the other.

Early ambulation is beneficial and the patient should get out of bed on the first or second postoperative day. This results in a smoother and more rapid convalescence even though it is difficult to demonstrate statistically that it decreases the incidence of complications such as phlebitis or thrombosis. There should be no rigid rule concerning the time at which a patient should be forced to get out of bed. The presence of drainage tubes, a stomach tube, or intravenous fluids should not interfere with the patient's getting out of bed. Tubes can be temporarily clamped and disconnected, or the bottles to which they are attached can be moved with the patient.

Emphasis should also be placed on movement of the shoulder girdle on the operated side. Beginning a day or two after operation, the patient is encouraged to move the arm on the operated side, particularly to elevate the arm. By the time the patient leaves the hospital, on about the tenth postoperative day, he should be able to extend the arm at full length above the head. If this relatively minor detail of postoperative care is neglected, the patient is apt to hug his elbow to the operated side, which will soon result in a stiff shoulder, especially in elderly people. Many painful months will then be spent trying to regain full use of the shoulder joint.

USE OF NASOTRACHEAL ASPIRATION

Nasotracheal aspiration is indicated whenever the patient's cough proves ineffective in clearing secretions from the tracheobronchial

Left heart failure may also be responsible for pulmonary edema.

Postoperative pulmonary edema may result from overtransfusion with blood, plasma, or a plasma substitute [2, 3]. If the circulating blood volume cannot be measured by the dye method, the clinical recognition of an excessive circulating blood volume is not simple. The patient's face may be flushed and the superficial veins distended. Perhaps an increase of the systemic venous pressure is the best clue to the condition. Indeed, the clinical condition is somewhat similar to that of congestive heart failure. The treatment is immediate venesection with the withdrawal of sufficient blood to reduce the blood volume to normal.

In addition to the specific measures referred to above, the patient should be maintained in a semierect position and given oxygen. Positive-pressure breathing may be beneficial and should be employed if all other measures fail, but it should be supervised by an experienced person.

TREATMENT OF POSTOPERATIVE INFECTION

There is little danger of infection of the pleural or peritoneal cavities in esophageal resections if soiling is avoided, and if the esophagojejunal or esophagogastric anastomosis is properly performed with the maintenance of a good blood supply at the anastomotic suture line. Following a pneumonectomy, a large dead space is left which constitutes a potential field for infection. At the conclusion of the operation this is filled with air which becomes gradually replaced after operation with serosanguineous fluid. The dead space and the collection of fluid constitute a violation of the usual rules of good surgical technic, and yet they are unavoidable. If infection does occur and the pleural effusion becomes purulent, it must be drained. If this happens early in the postoperative course, or the patient's general condition is precarious, drainage is best accomplished by the closed tube method. This can be done most simply by inserting a catheter in an intercostal space and connecting the catheter with the closed drainage system that has been described above. Later on, it will

usually be found advisable to convert this closed drainage to open drainage with large tubes inserted through the bed of a resected rib. Such open drainage can be established primarily if the fluid is markedly purulent and if the mediastinum is stable.

In postoperative empyemas, when no pulmonary tissue has been resected, drainage alone should be sufficient to allow the empyema cavity to heal. In lower lobe lobectomies, the establishment of open drainage is sometimes sufficient to result in healing from obliteration of the cavity by elevation of the diaphragm, shift of the mediastinum, and expansion of the remaining pulmonary tissue on the operated side. If healing does not occur promptly, the ribs overlying the empyema cavity should be resected subperiosteally. Following upper lobe lobectomies, a partial upper thoracoplasty may be necessary to obliterate the empyema cavity. Drainage of any empyema following a pneumonectomy invariably necessitates the performance of a thoracoplasty in order to obliterate the empyema cavity.

MANAGEMENT OF BRONCHOPLEURAL FISTULA

A bronchopleural fistula is rare following the operation of lobectomy. It constitutes, however, a serious postoperative complication in a small percentage of cases following pneumonectomy. Fortunately, it rarely occurs early in the postoperative period. It becomes evident most frequently twelve to sixteen days after the operation. The typical symptom produced by such a fistula is the coughing up of serosanguineous material that is similar in appearance to the pleural effusion. This may begin as slight hemoptysis or the coughing of pink frothy material. Confirmation of the presence of the fistula is obtained by having the patient lean toward his unoperated side. This maneuver will produce an increase in the expectoration of the characteristic pinkish fluid. The maneuver should be done cautiously so as not to flood the tracheobronchial tree with fluid and so drown the patient. Sometimes the opening between the bronchus and the pleural cavity apparently develops suddenly when the patient is lying down. This results in a paroxysm of coughing and ex-

of sodium by the intravenous route is inadvisable in the immediate postoperative period, because it will result in the retention of sodium and water and the production of edema [6, 8]. The edema, of course, will be most pronounced in the tissues injured by operation, and is particularly undesirable where there are important anastomotic suture lines, as in an esophagogastric anastomosis, or in the crucial suture line closing a bronchial stump.

NUTRITION

See Volume I, Chapter 9, for a general discussion of postoperative nutrition.

POSTOPERATIVE COMPLICATIONS

CARDIAC COMPLICATIONS

One of the commonest postoperative complications in elderly patients is auricular fibrillation, which usually appears during the first two or three postoperative days, but may occur at any time during the first week. Conversion to normal rhythm may take place spontaneously; if not, the fibrillation should be treated. If there are no signs of congestive failure, an attempt may be made to convert to normal rhythm by employing quinidine sulphate. If there is congestive failure or if the quinidine does not restore normal rhythm promptly, the patient should be digitalized rapidly. We use Lanatoside (Cedilanid) 1.6 mg. intravenously, followed by a maintenance dose of 0.1 to 0.2 mg. of digitoxin daily by mouth.

Disturbance of cardiac rhythm has been very rare in the authors' experience. Coronary thrombosis postoperatively is also fortunately rare and should not occur in the postoperative period more frequently than at any other time, provided the patient is adequately hydrated and that hemoconcentration is avoided. Patients with hypertension do not require any particular deviation from the routine postoperative treatment.

CAUSE AND TREATMENT OF PULMONARY EDEMA

Pulmonary edema is more likely to occur following a pneumonectomy than after other types of thoracic operations. After removal

of one lung, twice as much blood passes through the bed of the remaining lung. The pulmonary vascular bed of the remaining lung is, of course, easily able to accommodate this increased blood flow under conditions of moderate activity, even in elderly patients with some impairment of cardiac and pulmonary function. However, in the immediate postoperative period intrathoracic pressure relationships have not yet stabilized. Under these circumstances the increased blood flow and the increased volume of blood in the remaining lung provide favorable conditions for the development of pulmonary edema from relatively minor causes which, later in convalescence, would not produce pulmonary edema.

The common causes of postoperative pulmonary edema are: (1) an excessive serosanguineous pleural effusion, (2) left heart failure, and (3) the administration of excessive amounts of intravenous fluids. These conditions may exist in combination or singly. The relationship between a large collection of fluid in the pleural cavity following pneumonectomy and pulmonary edema in the remaining lung is not clear. The fluid may cause mechanical embarrassment of the heart, or the hydrostatic pressure of the fluid in the pleural cavity may compress the pulmonary veins, thus increasing pulmonary capillary pressure. The condition is aggravated with the patient in the recumbent position and alleviated when he is sitting up. It is best treated by withdrawing the serosanguineous fluid. While the fluid is being withdrawn, a somewhat smaller quantity of air should be injected, to leave the patient with a slightly negative intrapleural pressure. If the volume of the serosanguineous fluid is large, and particularly if it has a high hematocrit, a blood transfusion should be given, especially if the pulse rate is rapid and the hematocrit of the circulating blood below normal. Such a blood transfusion, if given slowly, will not result in a recurrence of the pulmonary edema. It will, on the contrary, restore the circulating mass of hemoglobin to its normal value, and thus make oxygen available to the tissues at a slower circulation rate, which in turn will diminish the work of the heart.

Left heart failure may also be responsible for pulmonary edema.

Postoperative pulmonary edema may result from overtransfusion with blood, plasma, or a plasma substitute [2, 3]. If the circulating blood volume cannot be measured by the dye method, the clinical recognition of an excessive circulating blood volume is not simple. The patient's face may be flushed and the superficial veins distended. Perhaps an increase of the systemic venous pressure is the best clue to the condition. Indeed, the clinical condition is somewhat similar to that of congestive heart failure. The treatment is immediate venesection with the withdrawal of sufficient blood to reduce the blood volume to normal.

In addition to the specific measures referred to above, the patient should be maintained in a semierect position and given oxygen. Positive-pressure breathing may be beneficial and should be employed if all other measures fail, but it should be supervised by an experienced person.

TREATMENT OF POSTOPERATIVE INFECTION

There is little danger of infection of the pleural or peritoneal cavities in esophageal resections if soiling is avoided, and if the esophagojejunal or esophagogastric anastomosis is properly performed with the maintenance of a good blood supply at the anastomotic suture line. Following a pneumonectomy, a large dead space is left which constitutes a potential field for infection. At the conclusion of the operation this is filled with air which becomes gradually replaced after operation with serosanguineous fluid. The dead space and the collection of fluid constitute a violation of the usual rules of good surgical technic, and yet they are unavoidable. If infection does occur and the pleural effusion becomes purulent, it must be drained. If this happens early in the postoperative course, or the patient's general condition is precarious, drainage is best accomplished by the closed tube method. This can be done most simply by inserting a catheter in an intercostal space and connecting the catheter with the closed drainage system that has been described above. Later on, it will

usually be found advisable to convert this closed drainage to open drainage with large tubes inserted through the bed of a resected rib. Such open drainage can be established primarily if the fluid is markedly purulent and if the mediastinum is stable.

In postoperative empyemas, when no pulmonary tissue has been resected, drainage alone should be sufficient to allow the empyema cavity to heal. In lower lobe lobectomies, the establishment of open drainage is sometimes sufficient to result in healing from obliteration of the cavity by elevation of the diaphragm, shift of the mediastinum, and expansion of the remaining pulmonary tissue on the operated side. If healing does not occur promptly, the ribs overlying the empyema cavity should be resected subperiosteally. Following upper lobe lobectomies, a partial upper thoracoplasty may be necessary to obliterate the empyema cavity. Drainage of any empyema following a pneumonectomy invariably necessitates the performance of a thoracoplasty in order to obliterate the empyema cavity.

MANAGEMENT OF BRONCHOPLEURAL FISTULA

A bronchopleural fistula is rare following the operation of lobectomy. It constitutes, however, a serious postoperative complication in a small percentage of cases following pneumonectomy. Fortunately, it rarely occurs early in the postoperative period. It becomes evident most frequently twelve to sixteen days after the operation. The typical symptom produced by such a fistula is the coughing up of serosanguineous material that is similar in appearance to the pleural effusion. This may begin as slight hemoptysis or the coughing of pink frothy material. Confirmation of the presence of the fistula is obtained by having the patient lean toward his unoperated side. This maneuver will produce an increase in the expectoration of the characteristic pinkish fluid. The maneuver should be done cautiously so as not to flood the tracheobronchial tree with fluid and so drown the patient. Sometimes the opening between the bronchus and the pleural cavity apparently develops suddenly when the patient is lying down. This results in a paroxysm of coughing and ex-

pectoration of large amounts of fluid. Fortunately, the patient will spontaneously assume the erect position. In this position, the pleural effusion will gravitate toward the most dependent part of the pleural cavity away from the bronchial opening.

As soon as a diagnosis of a bronchopleural fistula is made, all the fluid possible must be aspirated from the pleural cavity. This is best done through a needle in the eighth or ninth interspace in the posterior scapular line while the patient is erect. It is not necessary to replace the fluid with air, as air can easily enter the pleural cavity through the fistula. The aspiration should be repeated in 12 or 24 hours, and at intervals thereafter if the fluid reaccumulates, as shown by the patient's expectoration of the material, or as seen in a roentgenogram of the chest. If the fistula is of considerable size, it will make the patient dyspneic because of the to-and-fro movement of air through the fistula with respiration. During inspiration, air not only enters the good, remaining lung through the larynx but also through the fistula communicating with the opposite pleural cavity. Similarly with expiration, some of the expired air passes through the fistula into the pleural cavity. This movement of gases through the fistula will result in a diminished concentration of oxygen and an increased concentration of carbon dioxide in the alveolar air, with resultant dyspnea. If the fistula is of such a size that the patient is dyspneic, there is nothing to be gained by delaying definitive treatment.

The presence of a bronchopleural fistula creates an avenue for infection of the pleural cavity. When the fistula persists, infection of the pleural space is almost inevitable. When infection occurs, it should be treated promptly by open drainage and antibiotic therapy. The latter, however, will not prevent infection of the pleural space in any case of persistent fistula.

Attempts at closure of the fistula by direct suture will inevitably fail. The proper method is first to establish open drainage of the pleural cavity and then to perform an 8 or 9 rib thoracoplasty to obliterate the pleural space completely. Open drainage is best established by excising 8 to 10 cm. of the eighth or ninth rib posteriorly together with the

periosteum and pleura. The operation should be performed under local anesthesia with the patient sitting up. If it appears desirable, a similar length of the rib above or below the one resected can also be removed together with the intervening intercostal muscle bundle. The object is to create an opening large enough to provide easy access to the pleural cavity for packing. The pleural cavity is then packed from top to bottom with a long length of a wide gauze roll. The wound edges are covered with petrolatum gauze strips to prevent the gauze packing from becoming adherent to the wound. The original packing can usually be left in place for forty-eight hours, but should be changed daily thereafter. If the operative wound has been made large enough, the daily packing can be performed without discomfort to the patient. In our experience, open tube drainage is less effective in relieving the patient's symptoms of cough and dyspnea than the method of packing described above. Irrigations, of course, should never be employed because of the danger of the irrigating fluid entering the tracheobronchial tree by way of the fistula.

As soon as the patient's condition warrants, a thoracoplasty should be performed. It is best done under general anesthesia with an intratracheal tube in place. Because the mediastinum is stabilized by this time, a complete 8-rib or 9-rib thoracoplasty can be performed in one stage without producing any dangerous paradoxical motion. The packing will no longer be necessary following the thoracoplasty, and prompt healing of the fistula and the empyema cavity should result.

PHLEBITIS AND THROMBOSIS

Phlebothrombosis of the femoral venous system may occur after extensive thoracic operations. Because of the possibility of pulmonary embolism, it is a particularly hazardous complication following the removal of one lung. It is apparent that a pulmonary embolus of a size that might be tolerated by a patient with two lungs may prove fatal after a pneumonectomy.

The phlebothrombosis should be treated as soon as it is recognized, by the use of anti-coagulants or vein ligation. When one lung has been removed, we advocate vein ligation.

We make it a practice to ligate both superficial femoral veins even though the symptoms may be confined to one side. The usual technic is employed, with aspiration of any

clot that may be present. Elastic bandages are applied to the lower legs postoperatively, and the patient is allowed, and urged, to continue to be out of bed and walking.

Treatment of Neoplasms of the Trachea and Its Bifurcations

O. Theron Clagett,
Herman J. Moersch,
and
John H. Grindlay

Serious pathologic processes involving the trachea occur rarely, which is fortunate because of the vital role of the trachea in respiration. It is remarkable that the increased incidence of tumors involving the bronchi that has been apparent the last twenty years has not been accompanied by a similar increase in tumors of the trachea since the bronchi and trachea are similar anatomically. Because of their rarity and because a direct surgical attack on lesions of this vital organ has not seemed feasible, tumors of the trachea have received little attention even by endoscopists and thoracic surgeons. Treatment of these tumors, when they have occurred, has been limited to endoscopic removal of the intraluminal tumor mass when possible, the implantation of radon seeds, and roentgen therapy. Although such treatment has been successful in temporarily relieving difficulty in breathing in many cases, complete cure of malignant tumors has never been accomplished by these means.

Several developments in recent years have begun to dispel the spirit of defeatism that has prevailed regarding the possibility of a direct surgical attack on neoplasms of the trachea: (1) An increasing knowledge of the pathologic characteristics of tumors of the trachea and bronchi has shown that there is a considerable difference in the growth and behavior of the various types of tumors. Some, such as adenomas and cylindromas, grow slowly and do not metastasize readily, and

hence it seems likely that they might be treated successfully by wide local excision. (2) Confidence gained by extensive experience with pulmonary and intrathoracic operations makes operations on the trachea seem less formidable than in the past. (3) Developments in anesthesia and respiration of maintaining anesthesia and respiration during such operations. (4) A wide variety of surgical procedures performed on the trachea in experimental animals has demonstrated the feasibility of operations on this organ that had previously been considered impossible.

As a result of these developments, it now appears reasonable to give consideration to the possibility of surgical removal of the involved region in some tracheal tumors.

HISTORIC DATA

The first tumor of the trachea recorded in the literature was a fibroma found at necropsy and reported by Lieutaud in 1767. Langhans, in 1871, is credited with the first histologic description of a carcinoma of the trachea. The first diagnosis of tracheal tumors in living subjects was made by Schrotter in 1871 and Turck in 1886 with the aid of the laryngeal mirror. The first endoscopic diagnosis of a tracheal tumor was made by Killian in 1897. Statistically, tumors of the trachea are among the rare lesions of the body. Von Bruns, in 1898, was able to collect 31 cases of carcinoma of the trachea from the litera-

ture. D'Aunoy and Zoeller in 1931 [8] reported 351 tumors of the trachea in a review of cases reported in the literature. In 1938 Culp [6] reported a series of 433 primary tumors of the trachea, 147 (34 per cent) of which were carcinomas. According to Ellman and Whittaker [10], up to December, 1945, 507 cases of tumor of the trachea had been reported in the world literature. They divided these tumors into four groups as follows: simple tumors, 253; carcinomas, 187; other malignant tumors, 38; tumors of doubtful histology, 29.

Most of the published literature concerning tumors of the trachea consists of reports of one or two cases. Fisher [12] mentioned having observed six patients who had tracheal neoplasms among 20,433 patients seen in private practice. Tinney, Moersch, and McDonald [39] reported twenty-seven cases of tracheal tumors observed at the Mayo Clinic in the years 1921 through 1944. This is the largest series of cases of tracheal tumor from one institution reported in the literature.

Tumors can occur anywhere in the trachea. Culp mentioned that most of the cases reported in his review involved the posterior wall of the lower third of the trachea. Tinney, Moersch, and McDonald found 56 per cent of the tumors in their series involving the lower third of the trachea and noted that the anterior wall of the trachea was rarely the site of tumor formation. Tumors of the trachea occur predominantly in men, just as is true of bronchogenic neoplasms. According to Culp, 63 per cent occur in men. Most patients with tracheal tumors are from thirty to seventy years of age.

Ellman and Whittaker have recorded twenty different pathologic types of primary tracheal tumors. In the 507 cases of tracheal tumors collected by them, 225 (44.3 per cent) were considered malignant tumors. However, they classified adenomas and cylindromas of the trachea as benign tumors, whereas according to present pathologic criteria such tumors must be considered as malignant neoplasms. Tinney, Moersch, and McDonald in their report of twenty-seven cases found squamous-cell carcinomas in eleven, cylindromas in eight, adenocarcinomas in six, and hemangioendotheliomas in two.

PATHOLOGIC AND CLINICAL ASPECTS OF TRACHEAL TUMORS

Because of the extreme rarity of tumors of the trachea, it has been difficult to correlate the type of tumor with the clinical course of the patient. It is essential that the various types of tumors in the trachea be properly classified because of their widely variant growth factors. They can best be divided into those that are benign and those that are malignant.



Fig. 15-1. Papilloma of the trachea. The papillary projections of squamous epithelium may be seen. (Hematoxylin and eosin, $\times 50$)

Benign Tracheal Tumors

PAPILLOMA

The commonest benign tumor is the papilloma, which may be considered in two groups, namely, those occurring in children and those in adults. In both groups they are frequently associated with a similar tumor in the larynx and, in the occasional case, there may be involvement of the bronchial tree. The papillomas are usually multiple and may involve either a small or a large segment. The individual papillomas are usually small and pro-

duce a warty or cauliflower-like appearance, projecting into the lumen from the mucosa. The papilloma microscopically is made up of a core of connective tissue surrounded on three sides by slightly larger spindle cells that show some evidence of squamatization (Figure 15-1). A few mitotic figures are frequently seen. Although papillomas recur in children, they do not infiltrate, do not metas-

multiple, are benign, and may produce marked narrowing of the tracheal lumen with consequent symptoms. The mucosa overlying the projections of cartilaginous bone is intact. Histologically there is an intermingling of cartilage and bone (Figure 15-2). The actual bony cartilaginous outgrowths are hard and there has been considerable debate as to



Fig 15-2. Osteochondroma of the trachea showing the cartilage in bone. (Hematoxylin and eosin, $\times 45$)

tasize, and, therefore, must be considered benign. In adults, papillomas do not tend to be multiple, as they do in children, but they do tend to infiltrate and metastasize and should be considered potentially malignant. The microscopic appearance is similar to that of the papillomas seen in children. Regression is a prominent feature of papillomas in children when adolescence has been reached.

OSTEOCHONDROMA AND OTHER BENIGN TUMORS

Occasionally, osteochondromas will involve the trachea. These originate from the cartilaginous plates of the trachea and usually are

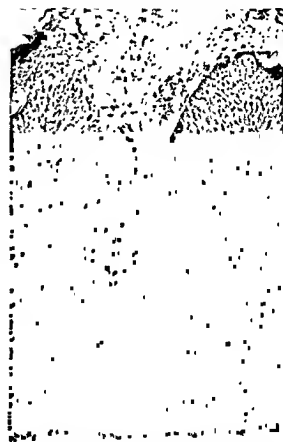


Fig 15-3. Squamous-cell carcinoma in situ of the trachea. The tumor cells have not infiltrated into the subjacent connective tissue. (Hematoxylin and eosin, $\times 125$)

whether these should be regarded as true tumors or merely exostoses.

Other benign tumors that are rarely encountered in the trachea are lipoma, hemangioma, and fibroma

Malignant Tracheal Tumors

SQUAMOUS-CELL CARCINOMA

This type of carcinoma is the most common and comprises 41 per cent of the series reported by Tinney, Moersch, and McDonald.

The tumors should be divided into two groups. In the first group, the malignant epithelial cells have not infiltrated the subjacent tissue (Figure 15-3). These are in situ carcinomas. As with carcinoma in situ elsewhere, until infiltration has occurred, metastasis does not develop. Grossly, such neoplasms can produce only slight thickening of the tracheal mucous membrane, and are usually difficult to diag-

CYLINDROMA

This is the second most common type of malignant tumor of the trachea. Tumors of this histologic type are seen in the mouth, nose, and throat, accessory paranasal sinuses, salivary glands, lacrimal glands, and, rarely, in the lungs. They apparently originate from the mucous glands in the wall of the trachea. As a consequence, the mucosa overlying a



Fig 15-4 Infiltrative squamous-cell carcinoma demonstrating the islands of malignant squamous epithelium deep in the tracheal wall (Hematoxylin and eosin, $\times 105$)



Fig 15-5 Cylindroma of the trachea demonstrating the cords of cells surrounding irregularly sized lumen filled with mucous secretion (Hematoxylin and eosin, $\times 115$)

nose. Because of the curability of in situ carcinoma of the trachea, local fulguration should effect a cure.

The second group consists of infiltrative squamous-cell carcinoma of the trachea which produces either a fungating or ulcerative growth, with invasion of the tracheal wall a common finding. The majority of the infiltrative carcinomas are of Grade III or Grade IV malignancy (Broders' classification) (Figure 15-4).

cylindroma of the trachea is usually intact. However, the tumor produces a bulge into the lumen of the trachea, resulting in diminution of the lumen's size. In all cases in which we have performed examination, the tumor has extended through the cartilaginous plates into the external fibrous layer of the trachea, and on occasions has involved adjacent structures. For instance, in one patient whom we have seen, the cylindroma invaded the thyroid gland. The appearance in the trachea may be

likened to an iceberg with the small top portion projecting into the lumen and the deep portion hidden in the tracheal wall.

The tumor cylindroma is composed of cells that form cords and tend to produce an appearance similar to that seen on the cut surface of Swiss cheese (Figure 15-5). Not infrequently, a stroma of mucoid connective tissue can be found between the epithelial strands. Such a stroma relates these tumors

similar in the trachea. Although the tumors are slowly growing, their course is relentless, with evidence of embolism late in the course. Since encapsulation of the tumor is seldom seen, surgical excision must include a portion of seemingly normal adjacent tissue.

ADENOMA OF CARCINOID TYPE

Adenomas of the carcinoid type, which are relatively common in the bronchus, may in-

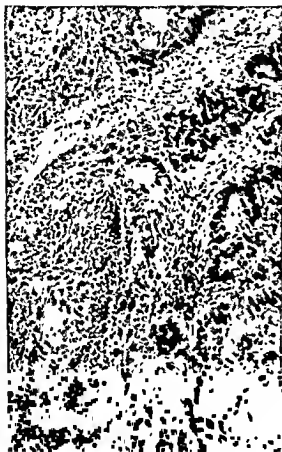


Fig. 15-6. Adenocarcinoma of the trachea. The carcinoma cells are forming acini (Hematoxylin and eosin, $\times 145$)



Fig. 15-7. Hemangioendothelioma of the trachea. The malignant cells appear to be forming immature blood vessels. (Hematoxylin and eosin, $\times 100$.)

to the mixed tumors of the salivary glands. Because of the rarity of the tumor in the trachea in comparison to other locations, the clinical course of these tumors can best be gauged by a study of cylindromas in other parts of the body. Such a study shows that in the mouth, nose, throat, and accessory paranasal sinuses these tumors are slowly growing but that, because of their infiltrative characteristics and their ability to metastasize by emboli, they are seldom cured. The clinical course is

involve the trachea secondarily but are seldom seen as a primary tumor. Most of the tumors that have been reported in the literature as adenomas are in reality cylindromas.

ADENOCARCINOMA

This is a small group; six such tumors were included in the twenty-seven cases reported by Tinney, Moersch, and McDonald. These tumors apparently originate from the surface mucosa and produce either a polypoid mass

or an excavating and ulcerating defect in the trachea. Microscopically these tumors produce acini and may produce mucus (Figure 15-6). They are very malignant.

HEMANGIOENDOTHELIOMA

There are a few malignant tumors that appear to be making blood vessels and for which the diagnosis of malignant hemangioendothelioma must be entertained (Figure 15-7). They are very rare.

SYMPTOMS OF TRACHEAL TUMORS

The symptoms of tracheal tumors are dependent primarily on mechanical factors

tients with tracheal tumor is regarded as being due to asthma for some time before the possibility of an obstructing tumor is considered. Logically one would expect wheeze to occur in patients with tracheal tumor and this symptom was encountered in 63 per cent of the Mayo Clinic series.

As would be expected, cough is a common symptom of tracheal tumor. At first the cough is dry and unproductive, but if the tumor ulcerates or obstructs drainage of the tracheobronchial tree, it may become productive. Hemoptysis had occurred in 44 per cent of the Mayo Clinic series. Hoarseness is a fairly frequent symptom of tracheal tumors and is

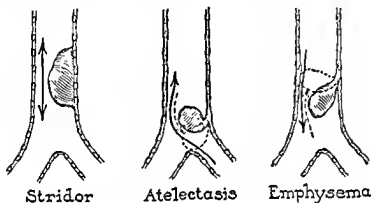


Fig 15-8 Mechanical factors responsible for some of the symptoms of tumor of the trachea. (From H. J. Moersch, *Proc Staff Meet, Mayo Clin* 21 410, 1946)

rather than on the pathologic characteristics of the tumor itself. These mechanical factors are illustrated in Figure 15-8. A tumor with a wide base, arising from the wall of the trachea and extending into the lumen, will interfere with both inspiration and expiration. A pedicled tumor, on the other hand, may cause obstruction to either inspiration or expiration. A study of Figure 15-8 will indicate the symptoms one might expect to occur in tracheal tumors. Owing to reduction in the size of the lumen, interference with the passage of air into the lung, with resulting dyspnea, would be expected. Clinically, dyspnea has been the earliest and most prominent symptom in cases of tracheal tumor and was found in 90 per cent of cases seen at the Mayo Clinic. The dyspnea may be either constant or paroxysmal and often is affected by change in position. Often the dyspnea in pa-

usually due to involvement of the recurrent laryngeal nerve by the peritracheal extension of the tumor lymph node involvement. Tumors of the trachea may involve the esophagus by direct extension and cause dysphagia.

DIAGNOSIS OF TRACHEAL TUMORS

Often physical examination in instances of tracheal tumor is entirely negative. A wheeze or stridor is significant when present. If the tumor obstructs either main bronchus, there may be physical signs of atelectasis or emphysema, depending on whether the tumor causes obstruction on inspiration or expiration. Roentgenograms of the thorax made in the usual way may show nothing of significance unless the tumor is causing obstruction of a main bronchus. Tomograms are useful and will usually outline tumors of the trachea

satisfactorily. Roentgenograms after instillation of iodized oil into the trachea may show the outline of a tumor of the trachea. Occasionally a tracheal tumor can be seen on direct laryngoscopy. Definite accurate diagnosis of tracheal tumors is best accomplished by bronchoscopic examination. There is considerable variation in the bronchoscopic appearance of tracheal tumors. Some are polypoid with a narrow pedicle, others flat and infiltrating. Some are ulcerated, others smooth and covered with normal tracheal epithelium. If the tumor is polypoid or pedunculated, the endoscopist may be able to remove all or most of the intraluminal projection of the tumor. Specimens of the flat, ulcerated, and infiltrating tumors can be removed by the endoscopist for histologic examination and the exact extent and location of the tumor can be ascertained in most instances.

TREATMENT OF TRACHEAL TUMORS

Treatment of tracheal tumors customarily has been left in the hands of the endoscopist. Available treatment has consisted of piecemeal removal of tissue projecting from the tracheal wall, diathermic cauterization of the base of the tumor, implantation of radon seeds, and externally administered roentgen therapy. Obviously, a more ideal treatment and one more in keeping with the accepted principles of surgery for neoplastic disease, would be a complete excision of the tumor with a surrounding margin of normal tissue and, if possible, the regional lymph nodes. Apparently, the hazards involved in an operation of this character on the trachea have precluded such treatment. A thorough review of the literature failed to disclose much evidence of efforts directed toward surgical excision of tracheal tumors.

Belsey, in 1946, reported a case of a woman of forty-two years who had an adenoma of the trachea. It had been treated for three years by cautery through the endoscope and by roentgen therapy. Belsey resected the lateral wall of the thoracic portion of the trachea and repaired the defect with a spiral of steel wire to maintain the lumen of the trachea covered by a patch of fascia from the thigh. The patient recovered but Belsey's

report does not indicate the course of events after two weeks.

In 1949 Rob and Bateman [35] reported four cases in which operation was performed on the cervical portions of the esophagus and trachea. In one case operation was performed for carcinoma of the thyroid and in three for carcinoma of the hypopharynx and upper part of the esophagus. None of these operations involved the intrathoracic portion of the trachea. In the reconstruction of the cervical trachea in these cases, fascia and tannum gauze were used. One patient was well after a year, one died in six months, one in five months, and one in four weeks after operation. Jarvis [23] mentioned one patient in whom a cylindroma was excised from the thoracic portion of the trachea just below the sternal notch. Tracheal continuity was maintained with a stainless steel tube. After one year the tube was removed. Within three weeks stenosis of the trachea made replacement of the tube necessary. This patient died thirty-three months after operation, of generalized pleural and pulmonary metastases. Holmes [21] reported a patient with trauma to the cervical portion of the trachea, with stenosis, for which insertion of a metal tube was required for maintenance of an airway.

In 1948 Longmire [30a] reported on the use of a lucite tube in repairing a tracheal defect. Postoperatively, the patient moved to Texas. About eight years later another surgeon removed the lucite prosthetic stent and was able to perform a primary anastomosis of the tracheal edges, which had become elongated throughout the years, as was demonstrated by Pressman and Simon (1958).

In 1948 Gibbon [14] reported the case of a patient in whom excision of a bronchial adenoma required resection of the left main bronchus and a portion low on the trachea. The defect in the trachea was successfully closed with a pedicled flap of parietal pleura wrapped around a piece of costal cartilage. Although the operation was a palliative procedure, the patient nevertheless had a year of life after the operation without dyspnea, and a total survival after operation of approximately fifteen months.

In 1958 Exequiel Lira [30] resected the trachea in two patients bearing cancer of the

upper portion of the trachea, and infringed upon the larynx. The procedure (Figure 15-9) required the performance of a partial laryngectomy and a transsternal tracheostomy, which functioned satisfactorily.

Our clinical experience with surgical resection of tumors of the trachea consists of three patients for whom resection of a portion of the trachea was performed. A brief resume will serve to illustrate the problem involved.

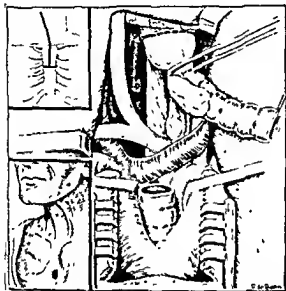


Fig. 15-9. Technic for the performance of a laryngectomy and a transsternal tracheostomy. (From E Urra [30], courtesy Archivos Sociedad de Cirujanos de Chile)

The first patient was a forty-nine-year-old man who presented a history of cough of three years' duration. Bronchoscopy revealed a large tumor mass almost filling the lower part of the trachea. This tumor (a cylindroma) was removed bronchoscopically, with immediate relief of wheezing and dyspnea. During the next six years, bronchoscopy with excision of recurrent tumor and coagulation of the base was performed twelve times. The tracheal tumor had been treated with roentgen rays. During these years the patient's general condition remained good. Metastasis did not develop.

In spite of the bronchoscopic removal of the intraluminal portion of the tumor, the lumen of the trachea gradually decreased until it measured only 2 mm. in diameter. Dilatation of the trachea at the site of nar-

rowing was performed, with some relief. Careful measurement disclosed that the distance from the trachea to the proximal margin of the tumor was 7.5 cm. and the distance from the distal edge of the tumor to the carina was 3.5 cm. Tomograms revealed marked narrowing of the lower part of the trachea and a small extratracheal mass. Severe wheezing and dyspnea recurred. The risks involved in attempting surgical resection of the trachea and reconstruction of an adequate airway were discussed frankly with the patient. He requested that the operation be attempted.

Anesthesia for operation presented a problem because the tracheal lumen was so narrowed that there was not an adequate airway for anesthetization. Therefore, after topical cocaineization of the pharynx, a Negus bronchoscope was introduced and with some difficulty passed through the strictured area into the left main bronchus. Nitrous oxide, oxygen, and ether anesthesia was then administered through the bronchoscope.

A right posterolateral incision was made. Segments of the fourth and fifth ribs were resected and the pleural space opened. The trachea and tumor was dissected out and mobilized without opening the left pleura. Circular incisions were made through the trachea above and below the tumor, completely freeing the segment of trachea containing the tumor. A polyethylene tube of suitable size and length was selected for insertion into the trachea to bridge the gap between the two ends of the trachea. Silk sutures were placed in the cut edge of the proximal and distal ends of the trachea, so that the tracheal ends could be approximated as closely as possible after the tube had been inserted. When the preparations had been completed, the bronchoscope was withdrawn from the left bronchus and lower part of the trachea. The segment of trachea and tumor was removed, the polyethylene tube was inserted, and the bronchoscope reinserted through the polyethylene tube into the left bronchus. This procedure was accomplished quickly and without difficulty.

Attempts to approximate the ends of the trachea as closely as possible with the previously placed silk sutures were unsuccessful, because the tissues at the lower end of the

trachea were weak and friable and the sutures pulled out. It was finally necessary to sacrifice the lower end of the trachea, the carina, and the right lung and restore the airway with a long polyethylene tube connecting the upper part of the trachea with the left main bronchus. The polyethylene tube was secured at each end with silk ligatures. There was no leakage of air. The mediastinal pleura was repaired, and the operative site was irrigated thoroughly with saline solution. Two hundred thousand units of penicillin were left in the pleural space. Tracheostomy was performed.

The postoperative course the first four days was uneventful. The temperature was only slightly elevated. The patient was able to eat without difficulty and to talk when the tracheostomy tube was closed. Secretions in the tracheobronchial tree required rather frequent aspiration. The left lung was clear on roentgenographic examination until the third day, when patchy regions of bronchopneumonia appeared. In spite of antibiotics and aspiration of the tracheobronchial tree, the bronchopneumonia progressed and on the sixth day the patient died of respiratory failure.

Post-mortem examination revealed that the plastic tube was not properly placed. It partially blocked the left upper-lobe bronchus and was undoubtedly responsible to a large extent for the bronchopneumonia in the left lung. There was no evidence of infection in the mediastinum or right pleural space. No residual tumor was found. (This case was previously reported by us in 1948 [5]).

A second patient, a sixty-year-old woman, had been well until four weeks previously, when she had had influenza and a dry cough. Three weeks before admission, hemoptysis had developed. Roentgenograms elsewhere had been reported "negative" but she had been hospitalized and treated with antibiotics. In spite of treatment she had become worse, and wheezing, severe dyspnea, increasing hemoptysis, and cyanosis had developed.

On admission to the Clinic she was hospitalized immediately. She was cyanotic and there was marked wheezing. Roentgenograms of the thorax were interpreted as showing an indefinite soft-tissue shadow low in the right pulmonary field. Other laboratory studies were noncontributory. Bronchoscopy was per-

formed. A large polypoid tumor was found on the right lateral and posterior walls of the lower end of the trachea. Most of the intratracheal portion of the tumor was removed



Fig. 15-10. Cylindroma of lateral wall of trachea, lying just above azygos vein and posterior to superior vena cava, in a sixty-year-old woman.

endoscopically. On pathologic examination the tumor proved to be a cylindroma of the trachea. Bronchoscopy was repeated, and the remainder of the tumor was removed. The patient was completely relieved of all her symptoms. Tomograms indicated a small tumor mass outside the tracheal wall at the site of the lesion. Excision of the tumor was advised. Figure 15-10 reveals the presence of



Fig. 15-11. Cylindroma of the trachea. Azygos vein divided and pleura reflected from cylindroma.

the tumor of this patient. Figure 15-11 shows the division of the azygos vein and Figures 15-12 and 15-13 illustrate the resultant defect after the removal of the tumor and the method of its repair. The patient remained well for the first postoperative year.



Fig. 15-12. Cylindroma of the trachea. Defect in lateral wall of trachea after excision of cylindroma. Intubation tube visible in tracheal lumen.

The third patient was a fifty-nine-year-old male whose symptoms consisted of a slight cough with occasional hemoptysis. Roentgenograms of the thorax did not reveal any abnormalities. Bronchoscopy revealed a flat, ulcerating lesion on the right lateral wall of the middle third of the trachea. A biopsy



Fig. 15-13. Cylindroma of the trachea. Repair of tracheal defect with wire-reinforced fascial patch.

revealed squamous-cell carcinoma, Grade IV.

Figure 15-14 shows the tumor exposed at thoracotomy. It was located on the right lateral wall of the trachea near the upper limit of the intrathoracic portion of the trachea. Several lymph nodes adjacent to the



Fig. 15-14. Squamous-cell carcinoma of right lateral wall of middle part of the trachea lying posterior to the superior vena cava in a fifty-nine-year-old male.

tumor were obviously involved with carcinoma. The right recurrent laryngeal nerve could not be mobilized from the tumor and was sacrificed. The involved lymph nodes, the tracheal tumor, and a margin of normal



Fig. 15-15. Squamous-cell carcinoma of the trachea. Defect in lateral wall of trachea after excision of carcinoma. Intubation tube visible in tracheal lumen.

trachea were excised. This required resection of more than half the circumference of the trachea and left a defect about 4 cm. long (Figure 15-15). The intratracheal tube

around the repaired trachea. The mediastinal pleura was repaired. Tracheostomy was performed. The postoperative course was satisfactory. The tracheostomy tube was removed on the tenth postoperative day. The patient was dismissed three weeks after operation.

Bronchoscopy one year later revealed some granulation tissue and secretion around both ends of the polyethylene tube. The tube was in good position but had loosened slightly. The patient remained well, mild symptoms being promptly controlled with antibiotics.

While it is impossible to draw any far-reaching conclusions from this series of three patients, this experience does demonstrate that many of the technical problems that have prohibited operations on the trachea in the past have been overcome and that in some instances, at least, tumors of the trachea can be removed successfully.

EXPERIMENTAL STUDIES

The following statements appear to be warranted as a result of our laboratory studies:

1. Abnormal retention of respiratory secretion does not occur because of the presence of a snugly fitting polyethylene tube in the normal dog's trachea or main bronchus.

2. Polyethylene tubes of the proper size and design cause minimal local irritation and few or no symptoms in dogs, even over a period of years

3. When no resection is performed, tubes that are placed in the trachea or bronchus are well tolerated but may become dislodged or cause irritation if they do not fit snugly. Clinically, when resection is impractical, the procedure of insertion of a tube for provision of an airway through the diseased portion of trachea may be useful as a palliative operation.

4. Portions of the trachea consisting of the entire circumference and 1 to 2 inches (2.54 to 5.08 cm.) long may be removed from dogs and an airtight anastomosis with interrupted sutures performed with facility and speed over specially designed, molded polyethylene tubes. Ridges at the ends of the tube on the outside make unnecessary circular ligatures, which might result in necrosis and leakage. The intercartilaginous membrane



Fig. 15-16. Squamous-cell carcinoma of the trachea. Polyethylene tube in place in the tracheal lumen.

was withdrawn temporarily and a polyethylene tube of appropriate size and length was inserted to bridge the defect in the trachea. This was secured in place with silk ligatures (Figure 15-16). A patch of fascia obtained from the right thigh was then sutured over the defect with interrupted silk sutures (Figure 15-17). A sheet of Gelfoam was wrapped



Fig. 15-17. Squamous-cell carcinoma of the trachea. Fascial flap sutured over the defect in the tracheal wall.

stretched over the ridge prevents leakage of air.

5. Significant amounts of cartilage do not appear to form in the scar-tissue bridge between ends of trachea if a gap is left at the time of anastomosis. It would probably be unsafe, therefore, to remove tubes in clinical practice if the ends of trachea were not fairly closely approximated. Until other studies concerning methods of bridging the gap by surrounding the tube with various tissues and materials are completed, tubes should not be removed unless preparation is made for the insertion of a new tube if stridor develops.

6. Removal of the lower part of the trachea

and bifurcation appears to be well tolerated by dogs, even though in our studies the right lung was removed also. It is possible that the coughing reflex is impaired by removal of the bifurcation and that, if the operation were performed clinically, patients should be instructed to cough forcefully from time to time.

7. Approximation of the ends of trachea after resection, or of trachea and bronchial stump after removal of the lower trachea and bifurcation, may be facilitated in dogs by the simple expedient of slight flexion of the neck. The same manipulation may be useful in clinical surgery of the trachea.

Treatment of Benign Lung Tumors Including Pulmonary Cysts

Viking Olov Björk

An increasing number of benign lung tumors are being diagnosed owing to mass radiography. There are two principles that apply to the treatment of all benign lung tumors. (1) They should all be removed by operation. (2) The operation must be conservative, with preservation of as much normal lung tissue as possible.

GENERAL PRINCIPLES OF TREATING BENIGN PULMONARY TUMORS

Indications for Operation for Benign Lung Tumors

The reasons for advocating removal of all benign neoplasms of the lung are:

1. A lung tumor is proved to be benign only by microscopic examination. The x-ray appearance of a benign tumor cannot with certainty be distinguished from that of a malignant neoplasm. If, therefore, no biopsy can be obtained, the possibility always remains that a well-defined rounded tumor is a peripheral bronchogenic carcinoma or, very rarely, a sarcoma.

2. Certain benign tumors are potentially malignant.

3. A slowly growing benign tumor may cause obstruction of a bronchus with bronchiectasis and infection behind the obstruction.

4. A benign tumor may cause pressure on the heart, the great vessels, the esophagus, etc., thereby producing anatomic and functional disturbances.

Technical Principles for Resecting Benign Pulmonary Tumors

The main principle in the surgical treatment of benign lung tumors is to preserve as

much functioning normal lung parenchyma as possible. As the tumor is benign, the ideal treatment is to remove only the tumor itself, with no lung tissue at all. This ideal can be achieved:

1. By removing central bronchial tumors together with the infiltrated part of the bronchial wall in one block and performing a plastic repair of the resulting defect in the bronchial wall.

2. By enucleation resection of peripheral well-defined benign lung tumors.

3. A minimum of lung tissue is sacrificed when a benign lung tumor is removed by wedge excision or by segmental or subsegmental resection.

Some of these conservative operations are more time-consuming than lobectomies or pneumonectomies, but every effort must be made to preserve functioning lung tissue. The removal of a benign lung tumor can never in itself be an excuse for diminishing the patient's respiratory reserve to a degree where his activities are limited.

Anesthesia

Anesthesia for intrathoracic operations is discussed in Chapter 13. The technic of one-lung anesthesia, which is particularly suited for certain types of pulmonary tumors, is presented here.

The flexible double-lumen catheter constructed by Carlens for bronchspirometry has been used for one-lung anesthesia and continuous suction. It is considered ideal to prevent the "spilling over" of secretion during resection of "wet cases." The catheter (Figure 16-1) is made of rubber of approximately the same rigidity as an ordinary ure-

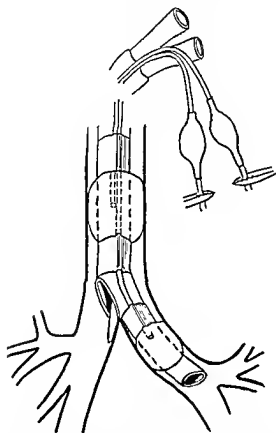


Fig 16-1. Resection of benign tumor of lung. Diagram of the double-lumen catheter in position. Note the small rubber hook that is automatically engaged by the carina

thral catheter and is provided with a small hook that is automatically engaged in the carina. The inner diameter of each lumen is 7 mm. in the catheter for men and 6 mm. in the one for women. The catheter is introduced under topical anesthesia. Its tip is curved so that it automatically enters the left main bronchus. It is then easy to feel when the rubber hook is engaged by the carina. After the cuffs are inflated, the anesthesia and suction can be applied to each lung separately. In case of sudden intrabronchial hemorrhage from a detached tumor during operation, the double-lumen catheter may be lifesaving.

Closure and plastic repair of the bronchus can be performed on the open bronchus without the use of bronchial clamps. The bronchus can easily be inspected and a small suction catheter may be introduced in the bronchial branches, which may be of help for orientation in patients with bronchial abnormalities. With the tube in place, a resection of the right lung, including the carina, can easily be carried out. The method has been used in more than five hundred cases. The advantages are best illustrated by the diagrams (Figures 16-2, 16-3, 16-4, 16-5, and

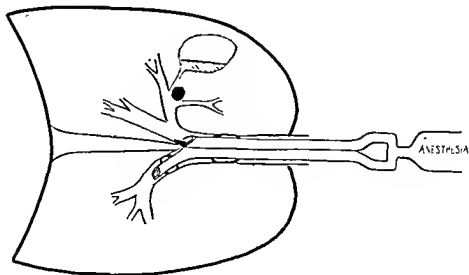


Fig 16-2. During the incision, both lungs are connected with the anesthesia machine.

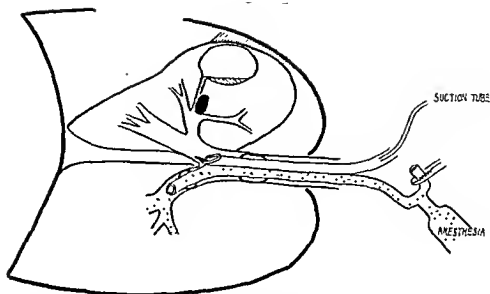


Fig 16-3. When the chest is opened, anesthesia is given to the nonoperated lung only. The right lung is atelectatic and immobile, increasing the operating space and facilitating the separation of the lung from the chest wall. Continuous suction is applied in the right bronchi.

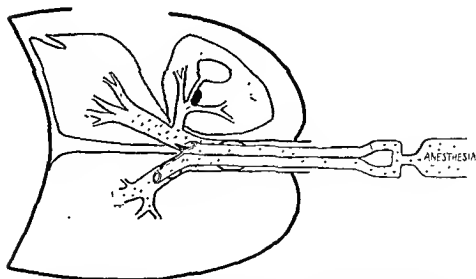


Fig. 16-4. After careful aspiration, both lungs are connected with the anesthesia machine as the separation of the lobes or segments is facilitated by the inflation of the lung.

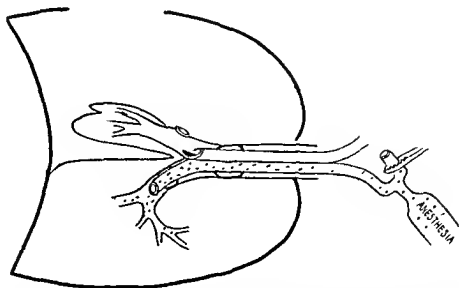


Fig. 16-5 Branchial closure is made on the open bronchus when the operated lung is disconnected from the anesthesia machine. No bronchial clamp is used.

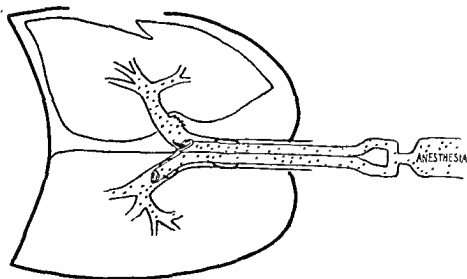


Fig. 16-6 After completion of the lobectomy, the remaining part of the right lung is inflated after careful aspiration and the anesthesia is continued on both lungs.

16-6) showing a patient with a bronchial adenoma in the right upper-lobe bronchus with an abscess behind the obstruction.

BENIGN CENTRAL BRONCHIAL TUMORS

Pathologic Classification

MESENCHYMAL BRONCHIAL TUMORS

Benign bronchial tumors may contain predominantly mesoblastic elements and are described under the names of chondroma, osteoma, fibroma, lipoma, fibrolipoma, angioma, myxoma, xanthoma, myoma, and myoblastoma. These mesenchymal bronchial tumors are comparatively seldom encountered in the main bronchi and are, therefore, of little clinical importance. They rarely turn malignant, but a few cases of fibrosarcoma, myxosarcoma, and chondrosarcoma of the bronchus have been described.

BRONCHIOMA

Tumors containing all the elements of the adult bronchus, although with an abnormal admixture, i.e., bronchiomas, are rarely found in the main bronchi. Only a few cases have been found of endobronchial bronchiomas (including one case at the Sabbatsberg Hospital). This malformation is fairly common among peripheral benign tumors and will be described under that heading.

ADENOMA

Adenoma is the most common type of benign central bronchial tumor. This subject is discussed in Chapter 17.

Clinical Features of Central Bronchial Tumors

Cough is the language whereby the bronchial tree complains of irritations from all causes. The most important first symptom is, therefore, the cough.

Hemoptysis is a common symptom of bronchial angioma and adenoma. In the Sabbatsberg Hospital, 45 per cent of such patients had hemoptysis.

Dyspnea may occur when the tumor is stenosing the bronchus, causing interference with air exchange. The onset of dyspnea is usually gradual and often seems out of pro-

portion to the degree of the associated atelectasis.

The duration of symptoms before the diagnosis is established is long. In bronchial adenoma an average delay of 8.4 months occurred. In the Sabbatsberg Hospital material, the duration of symptoms before a diagnosis of benign bronchial tumor was established was as follows (Carlens):

Duration of symptoms in years	0-1	1-2	2-3	3-5	5-11	11-16
Number of patients	22	8	4	11	11	3

Treatment of Benign Bronchial Tumors

TREATMENT BY BRONCHOSCOPY

Radical Treatment

Benign tumors situated in one of the main bronchi may be radically removed by bronchoscopy if they are pedunculated. Bronchoscopic removal of a submucous lipoma from the bifurcation of the trachea (Kernan) and of a pedunculated lipoma from the left main bronchus (Vinson and Pembleton [52]) has been reported. Fibrolipomas have also been removed by bronchoscopy (Myerson, Jackson, and Jackson, and McGlade). Surprisingly enough, a fibrosarcoma of the bronchus has been bronchoscopically removed (Pollack, Cohen, Borroni, and Gnassi), the patient being well after more than six years. Davidson [30] reported a patient with a pedunculated chondroma of the bronchus removed by bronchoscopy.

A radical removal of a bronchial adenoma by bronchoscopic electrocoagulation will rarely be possible, as 80 per cent of the tumors have a peribronchial extension. It is impossible to determine the exact size of this extrabronchial part of the tumor by x-ray examination, although laminagraphic studies may give some information. The only indication for an attempt at radical endoscopic removal is in the very rare cases where the tumor is entirely within the bronchus, attached by a long, slender pedicle. These patients are then bronchoscoped at intervals, and the most reliable test that the neoplasm has been completely eradicated is the absence

of tumor cells in biopsy specimens from the bronchial wall at the point of attachment of the tumor.

The majority of bronchial adenomas should not be treated solely by bronchoscopic methods (see Chap. 17).

Palliative Treatment by Bronchoscopy

Palliative treatment of bronchial tumors by bronchoscopy is indicated in an aged individual who is not a reasonable surgical risk.



tumor and make the lung as dry as possible before operation.

2. To make possible an exact localization of the attachment of the tumor to the bronchial wall.

3. To permit bronchographic demonstration of the irreversible damage to the distal portion of the lung as a result of prolonged bronchial obstruction.

4 To make the lung deflatable during an operation. An obstructed lung may be dis-



Fig 16-7. (Left) Bronchogram of adenoma in a thirty-nine year-old female obstructing the right main bronchus and most of the left main bronchus. The patient was then breathing only with the right upper lobe through an abnormal bronchus with the origin in the trachea 2 cm. above the carina. (Right) Diagram of the tumor in left illustration.

Palliative bronchoscopic treatment may also be indicated in some patients when the tumor involves the trachea, the carina, or both main bronchi

Preoperative Treatment by Bronchoscopy

In cases where a benign tumor is obstructing one main bronchus, a bronchoscopic clearing of the bronchus preoperatively is indicated for several reasons:

1. To improve drainage of the secretion and infected material dammed up behind the

tended, rendering the operation difficult owing to diminished operative space. One patient is reported (Massachusetts General Hospital Case 24202) to have died of massive hemorrhage from the base of the tumor (fibrosarcoma), which caused complete obstruction of the right bronchus and was detached from its base during an attempt to deflate the distended obstructed lung during operation.

The preoperative bronchoscopic clearing of the airways will improve the patient's general condition by improved drainage and

aceration of atelectatic parts. Furthermore, in some cases a more conservative operation may be used after preoperative bronchoscopic treatment. Figures 16-7, 16-8, and 16-9 illustrate this advantage.

TREATMENT BY BRONCHOTOMY

The direct opening of a major bronchus may sometimes be necessary to remove a pe-



Fig 16-8. Bronchograph after thirteen preoperative bronchoscopic electrocoagulation treatments that identified the origin of the tumor shown in Figure 16-7 (Compare with Figure 16-7 left)

dunculated tumor that cannot be extracted by bronchoscopy. One case of pedunculated bronchioma in the left main bronchus was excised through a bronchotomy by Husfeldt [20]. One-lung anesthesia with the double-lumen catheter will greatly facilitate the procedure. The exploratory incision is made through the noncartilaginous posterior wall when possible. Excision and exact hemostasis of a pedunculated tumor or of a hemangioma

may be performed. The bronchus is closed by edge-to-edge approximation with interrupted sutures of fine catgut. Even if the cartilaginous wall is to be sutured, sutures of fine catgut are preferred. By covering the suture with a pleural flap, air leakage is prevented. Postoperative suction is maintained through an intercostal catheter.

TREATMENT OF CENTRAL BRONCHIAL TUMORS BY LOCAL RESECTION OF BRONCHIAL WALL WITH THE TUMOR

The ideal treatment in the early cases of benign central tumors is to preserve all lung parenchyma, only removing the intra-bronchial

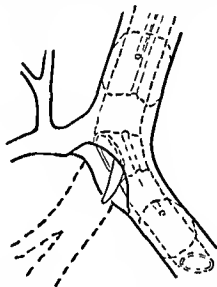


Fig 16-9. Diagram of the resected right lower and middle lobe including the carina and a small region of the left main bronchus. (Same patient as in Figures 16-7 and 16-8)

and extrabronchial part of the tumor in one block together with the infiltrated part of the bronchial wall, performing a plastic repair of the resulting defect in the wall.

In most patients with bronchial tumor (adenomas) it is necessary to perform a lobectomy, owing to the long-standing bronchial obstruction causing bronchiectasis. But in early cases, when the changes behind the tumor are reversible, the following treatment should be considered as giving the best functional result and preserving lung parenchyma:

1. If the tumor is large, causing atelectasis, most of the intrabronchial portion of the tumor should be electrocoagulated, giving a

free air passage with re-expansion of the atelectatic part of the lung, if possible, and drainage of accumulated secretion. The base of the tumor can then be clearly visualized and localized and the condition of the lung distal to the tumor can be investigated.



Fig 16-10 Diagram of an adenoma obstructing the right main bronchus, which reached the level of the carina before electrocoagulation

2. After some weeks the intrabronchial and extrabronchial part of the tumor sometimes can be removed in one block together with the infiltrated part of the bronchial wall. The defect in the bronchial wall can be repaired by suture of the edges end to end. If the defect is too large, a plastic repair with fascia lata or skin graft may be performed. The suture line should be covered by a pleural flap.

3. The scar of the suture line in a bronchial wall has a great tendency to shrink, causing a stricture. It is therefore necessary to follow the patient postoperatively, with dilatation through the bronchoscope if a scar develops, or the removal of granulomatous tissue. These dilatations could start one month after the operation and ought to be performed at weekly intervals in the beginning. When the tendency to shrink has ceased, the bronchial lumen will remain unchanged.

In some cases it is possible to do the local excision of the tumor without previous electrocoagulation. Figures 16-10 and 16-11 demonstrate such an instance in a twenty-one-year-old male whose bronchial tumor was treated by preliminary electrocoagulation that was followed by excision of the bronchial wall with extrabronchial part and the remaining intrabronchial part of the tumor in one block. The defect in the bronchial wall was sutured and thus the functioning tissue of the whole right lung was preserved (Figure 16-11).

TREATMENT BY LOBECTOMY AND PNEUMONECTOMY

Lobectomy and pneumonectomy are still the procedures of choice in the great majority of patients when there has been irreversible damage to the distal portion of the lung as a result of a prolonged bronchial obstruction.

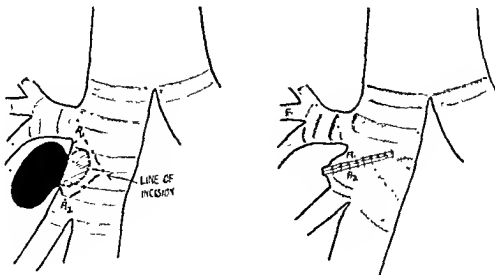


Fig 16-11. Adenoma obstructing the right main bronchus. Diagrams demonstrating repair of the defect in the bronchial wall of the patient shown in Figure 16-10.

In the Sabbatsberg material, nineteen patients had a pneumonectomy and twenty-three a lobectomy. Adjacent mediastinal nodes should also be removed for adenoma, as they occasionally are involved.

BENIGN PERIPHERAL LUNG TUMORS

Pathologic Classification

MESENCHYMAL TUMORS

Benign peripheral lung tumors may be mesenchymal: chondroma, fibroma, lipoma, fibrolipoma, angioma racemosum, myxoma, myoma, and xanthoma. They rarely turn malignant, and the most conservative operation has to be performed.

BRONCHIOMA

Bronchioma, earlier called chondroma, hamartoma, or hamartoma chondromatosum pulmonis, only recently and owing to mass radiography has become a common peripheral lung "tumor." More than one hundred cases have been reported. Bronchiomas may be considered as congenital malformations. They occur at all ages and have been found in a newborn infant.

There has been much discussion in the literature about the terminology. Most often the name chondroma has been applied (Hickey and Simpson [36], Klages, and others), but they are not pure cartilaginous tumors and chondroma is, therefore, not an adequate term. The term "hamartoma" was coined by Albrecht in 1904 with the following definition: "Hamartomas are tumorlike malformations in which occurs only an abnormal mixing of the normal components of the organs. The abnormality may take the form of a change in quantity, arrangement or degree of differentiation, or may comprise all three." Since Albrecht's description of the general group of hamartomas, this term has been adopted by Goldsworthy; McDonald, Harrington, and Clagett, Simon and Ballon, and others. Womack and Graham [55], however, suggested that all the pulmonary tumors that supposedly arose from the failure of embryonic bronchial buds to develop into normal structures should be designated as "mixed tumors of the lung." They should not be regarded as true teratomas.

Reviewing the fact that these tumors constitute a bronchial complex, with representatives of all the histologic elements contained in mature bronchi, the only logical term is bronchioma, which has been adopted at the Crafoord Clinic, where we have studied nine such patients.

Bronchioma may occur anywhere in the lung, but most commonly is found in the periphery beneath the pleura, sometimes attached to the pleura by a pedicle. Very few cases of endobronchial bronchiomas have been described.

The size may vary; the tumor may be as small as a bean or fill the entire thorax. The color is whitish and on palpation the growth is firm and hard, round or lobulated, and surrounded by normal lung. Only when occurring in direct relation to a bronchus, the growth is rather fixed; otherwise, it is without attachment to the lung and surrounded by a fine capsule of loose connective tissue. There is usually a compression atelectasis of the adjacent lung tissue.

Bronchiomas are benign and no metastases have been reported. One case of malignant degeneration (hamartoma osteochondromatosum pulmonis malignum) showing considerable cellular variations and invasion into mediastinal fatty tissue has been described.

ADENOMA

Bronchial adenomas were earlier considered to arise invariably in one of the larger bronchi. They may, however, occur in smaller bronchi not visible bronchoscopically, when they cannot preoperatively be distinguished from other peripheral benign lung tumors (see Chap. 17).

Clinical Features of Benign Peripheral Lung Tumors

Most of the benign peripheral lung tumors give no symptoms. Since the employment of mass radiography, an increasing number of benign silent lung tumors have been observed. No histologic diagnosis can be achieved before the operation. The roentgenographic shadow may represent a peripheral bronchogenic carcinoma, a metastatic tumor, adenoma, bronchioma, mesenchymal tumor, tuberculoma, or a fluid-containing cyst. If



Fig. 16-12. Roentgenograms demonstrating an xanthoma in the left lower lobe

calcification is found, the tumor is probably a bronchioma, a tuberculoma, or an echinococcus cyst.

As a peripheral carcinoma cannot be excluded with certainty (23 per cent of all bronchiogenic carcinomas have the appearance of a well-defined rounded shadow), the treatment in all such patients is operation. A biopsy for frozen section of the tumor is obtained during operation and the resection is carried out as conservatively as the microscopic diagnosis will permit.

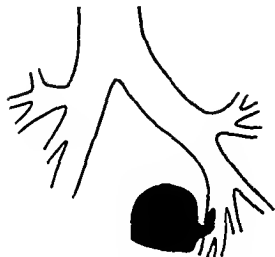


Fig. 16-13. Diagram of the xanthoma in the left lower lobe shown in Figure 16-12

Treatment of Benign Peripheral Lung Tumors

TREATMENT BY ENUCLEATION RESECTION

Enucleation resection is an operation in which the tumor is removed without sacrifice of lung tissue. The functional result, therefore, is the best possible. Enucleation resection should be considered in benign peripheral lung tumors without secondary lung damage, especially if the tumor is a bronchioma. In other cases, a segmental resection is most often preferred.

Bronchiomas are most suitable for enucleation, but other benign tumors may also be treated this way. (A case of xanthoma and one of peripheral bronchial adenoma are presented in Figures 16-12 through 16-17). Frozen sections of the tumor should be examined microscopically immediately, so that the nature of the tumor can be determined without question. If the neoplasm proves to be a sarcoma, a lobectomy is carried out; if a carcinoma is found, a lobectomy or pneumonectomy is performed.

Enucleation resection was outlined by Borelius in 1915 [15]. In a forty-year-old woman an accidental x-ray showed a well-defined rounded shadow in the left lower lobe, the



Fig 16-14 Photomicrograph of stained slide of the xanthoma in Figures 16-12 and 16-13 showing xanthoma cells distended with lipoid droplets, giant cells, and deposit of blood pigment. Although it was a benign tumor, postoperative hemorrhage killed the patient.

size of an orange. An incision was made through the lung parenchyma over the tumor (a bronchioma), which was easily enucleated. A considerable hemorrhage was encountered and controlled. The incision in the lung was sutured in layers, and recovery was uneventful.

This technic has been improved by Crafoord. In order to obtain a bloodless operative field, the artery, the vein, and the bronchus with the bronchial arteries to the involved lobe are dissected free and clamped with noncrushing forceps. Before the bronchus is clamped, the lung is rendered atelectatic, which is easily accomplished when one-lung anesthesia is used. The atelectatic lung tissue is then incised over the tumor. Large vessels in the wound can be dissected free and retracted out of the way, and the tumor is enucleated. Then the small vessels are carefully taken with hemostats and tied, and bronchial branches, opened when the lung is incised, are sutured or clamped and tied. A meticulous ligation of all bleeding points is essential in this technic. If a small artery is overlooked, causing hemorrhage into the bronchial tree, this may be fatal. (This happened in a case in which a neurofibroma was enucleated from the left lower lobe.) After the enucleation, the clamps are removed and



Fig 16-15. Bronchioma of the left upper lobe treated by enucleation resection (posteroanterior and lateral views).



Fig 16-16 Bronchioma of the left upper lobe (same patient as in Figure 16-15) Two months after the operation a small hematoma is still visible. At a later date the roentgenograms were normal.



Fig 16-17. Photomicrograph showing typical histologic pattern of bronchioma with cartilage, connective tissue, and columnar epithelial cells.

any further bleeding points are ligated and openings into the bronchial tree sutured. The lung is then usually sutured in layers to prevent the formation of a hematoma where the tumor was situated. In spite of these deep sutures, a hematoma will most often develop after the operation. Then the x-ray after the operation is very similar to the one before the enucleation. After some months, however, the hematoma will have been absorbed. Therefore, in some cases no suture of lung tissue has been performed after the enucleation. The incision in the lung tissue has been left open in order to facilitate the drainage and absorption of serum and blood accumulated in the space after the enucleation of the tumor. The aftercourse has been uneventful in these cases, and deep sutures for approximation are no longer used. The more anatomic subsegmental resection is, however, preferred.

TREATMENT BY WEDGE EXCISION

Wedge-shaped local excision is used in small peripheral benign lung tumors that are not sufficiently well demarcated from the surrounding lung parenchyma to permit an enucleation. In such cases (usually a mesenchymal tumor or a tuberculoma) the decision

has to be made if the more anatomic procedure of segmental or subsegmental resection is to be preferred (which is usually the case) to the wedge excision. If the tumor is small and situated subpleurally, and it is difficult to determine with certainty which segment is to be removed, the excision of a small wedge-shaped section from the peripheral portion of a lobe is preferred.

will provide an airtight and hemostatic closure. An approximation of the cut edges may sometimes be added.

TREATMENT BY SEGMENTAL OR SUBSEGMENTAL RESECTION

A segmental or subsegmental resection is the treatment of choice in most benign peripheral lung tumors. On the preoperative



Fig. 16-18 A case of angioma racemosum in the lateral subsegment of the posterior segment of the right upper lobe. (Left) Posteroanterior laminogram. (Right) Lateral laminogram. Note the fissure between the upper, middle, and lower lobes of the lower border of the tumor.

The lung is rendered atelectatic with the aid of the double-lumen catheter, using one-lung anesthesia, and the wedge-shaped section of lung containing the tumor is blocked off by means of two series of hemostatic forceps applied in succession and excised. No effort is made to isolate and ligate separately the pulmonary vessels or the bronchi individually. A ligation of the applied forceps

posteroanterior and lateral laminograms it is often possible to determine that an enucleation resection is not feasible by the irregular and unsharp demarcation of the tumor from the lung tissue. This is well illustrated in Figure 16-18 where the irregular shape of an angioma racemosum in the lateral subsegment of the posterior segment of the right upper lobe was found in a thirty-three-year-

old woman. There was no fissure between the upper lobe and the apical segment of the lower lobe. Therefore, a segmental resection of the posterior segment of the upper lobe was performed, although a resection of the lateral subsegment would have been sufficient. The recovery was uneventful.

The segmental bronchus is identified, isolated, and divided before the artery is divided, whenever possible. As few veins as possible are ligated at the hilar level. The proper segmental plane for dissection is disclosed as soon as gentle traction is applied upon the divided segmental bronchus and artery. In this plane the small venous tributaries empty into the main intersegmental vein, which is followed during the dissection. The larger tributaries may be clamped and even the smaller vessels may be clamped before they are torn across at their junction with the intersegmental vein, which is easily visible on the raw surface of the residual segments. The preservation of this vein is important; otherwise a passive congestion may occur in the segments left behind. If by frozen section the tumor proves to be a carcinoma, the lobe or lung must be removed.

TREATMENT BY LOBECTOMY AND PNEUMONECTOMY

Lobectomy and pneumonectomy are rarely used in treating benign peripheral lung tumors. However, if the tumor is large, with secondary disease in the lung tissue, this more extensive resection has to be done. In cases with sarcomatous degeneration in a mesenchymal tumor, a lobectomy will prove to be radical enough in nearly all patients, as the lymphatic system is not involved.

BRONCHOGENIC CYSTS

Pathology of Bronchogenic Cysts

Bronchogenic cysts possess an epithelial lining consisting of columnar or cuboidal cells that may or may not be ciliated. This lining may be smooth and regular or irregular and trabeculated. The walls of the cyst contain fragments of bronchial elements such as cartilage, smooth muscle, elastic tissue, and mucous glands in an irregular arrangement. These cysts may be single or mul-

tiples; they may or may not communicate with a bronchus.

Bronchogenic cysts may be congenital in origin, arising from an accessory bronchial bud. If the cysts appear in early infancy, if they are associated with anomalous blood vessels (large arteries may go from the aorta above or below the diaphragm to the cystic region), if they are associated with accessory or aberrant lobes of the lungs, if they occur between lobes or in the mediastinum near or attached by a stalk to the bifurcation of the trachea or to a main bronchus, they are considered to be congenital. If none of these criteria is found, it is difficult or impossible to determine if the cyst is developmental or acquired. Examples of acquired bronchogenic cysts are pulmonary abscesses with epithelization, or a cystic lobe behind a bronchial adenoma (sometimes called "cystic" bronchiectasis).

Clinical Features of Bronchogenic Cysts

Bronchogenic cysts may remain clinically dormant for indefinite periods, whether they have bronchial communication or not. Symptoms may first arise from secondary pulmonary changes such as bronchiectasis, which are very often associated with pulmonary cysts. There is usually some complicating factor causing the symptoms. The most common complication is infection with suppuration, causing cough and expectoration, usually following an acute respiratory infection with an attack of fever.

Hemoptysis is a common symptom and may vary from exsanguinating hemorrhages to blood-stained sputum.

Dyspnea may be extreme and due to a small or angulated communication between the cyst and the respiratory tract, with a valvelike mechanism so that on inspiration the air is drawn into the cyst and on expiration the air cannot escape. Thus, a positive pressure can be built up in the cyst, which becomes greatly distended, compressing adjacent lung tissue and dislocating mediastinal organs to the opposite side. This complication, as well as rupture of the cyst into the pleural cavity with resultant tension pneumothorax and empyema, may cause dyspnea, pain, dysphagia, stridor, or palpitation.

Diagnosis of Bronchogenic Cysts

The x-ray features are most important in the diagnosis of bronchogenic cysts. If the cyst contains fluid, the x-ray picture may suggest inflammatory consolidation, atelectasis, emphyema, or even solid tumor. When the cyst contains air, with or without a fluid level, it must be differentiated from an emphysematous bulla, loculated pneumothorax, pulmonary abscess, tuberculous cavitation, bronchogenic carcinoma, mediastinal tumor, and diaphragmatic hernia. The diagnosis is more difficult when pulmonary tuberculosis or bronchogenic carcinoma coexists with cystic disease of the lungs. A number of these patients have spent long periods in sanatoria. A few cases have been described in which a bronchogenic carcinoma developed within a pulmonary cyst (Graham and Womack; Moersch and Clagett).

Bronchoscopy must be performed, to exclude a bronchial neoplasm or stenosis as the cause of the cystic disease.

Bronchography is of value to demonstrate the commonly coexisting bronchiectasis. Furthermore, bronchoscopy and bronchography will demonstrate any bronchial abnormality that often is present in patients with congenital cysts. It may be of great importance to know of this abnormal bronchial anatomy before the operation.

Treatment of Bronchogenic Cysts

The treatment of all bronchogenic cysts is extirpation. At the time of operation some complication usually exists. In the very few cases in which the cyst is attached by a narrow pedicle or loosely to the parenchyma of the lung, a local excision will be possible. In most cases of bronchogenic cyst a lobectomy is the treatment of choice. Segmental resection or pneumonectomy must also be considered in a few cases owing to localization and distribution of the cystic disease. Attention must be paid to the commonly existing abnormal arteries going to the cystic region, as these may be of considerable size.

ALVEOLAR CYSTS OF THE LUNG

Pathology of Alveolar Cysts

The lining of alveolar cysts is composed of fibrous tissue and alveolar cells. These

cysts are acquired, and may be localized subpleural blebs or bullae, or part of a more generalized emphysema. Blebs are formed by the rupture of an alveolus directly beneath the pleura, with the escape of air into the areolar layer of the pleura. The air separates this areolar layer and the pleura from the underlying alveoli, and the extension of air may continue until arrested by some lobular septa. A bulla, on the other hand, results from the rupture of one alveolus into adjoining alveoli. With continued accumulation of air, a large air sac may form, compressing adjacent alveoli and stretching the pleura tightly over the expanding bulla. It may not be possible to distinguish large bullae and blebs grossly or microscopically and such a distinction is unimportant.

Localized blebs and bullae develop secondary to the production of a valvelike mechanism in the terminal bronchiole, often owing to scarring of the lung and pleura from old, healed tuberculosis. The fibrosis or a torsion on a terminal bronchiole acts as a valvelike mechanism, with trapping of air and distention of the alveolus. Edema of the mucosa of the bronchiole allows air to enter but its narrowed diameter during expiration may be sufficient to prevent the escape of the air.

Blebs or bullae may be part of a more generalized emphysema. Then the walls between the alveoli are destroyed so that several alveoli communicate to form one large air space. The amount of pulmonary capillaries is reduced, which in pronounced emphysema will result in arterial oxygen deficit. At that stage there is often found a hypertension in the pulmonary artery.

One of these emphysematous blebs or bullae may occupy an entire hemithorax. Much of the lung may be replaced by these giant bullous cysts, and the rest is compressed by them.

Clinical Features of Alveolar Cysts

The two most common symptoms of alveolar cysts are dyspnea and spontaneous pneumothorax. Infection and hemorrhage do occur but not as frequently as in bronchogenic cysts.

Diagnosis of Alveolar Cysts

The diagnosis is made roentgenographically. The cyst appears as an area of decreased density with a fine border traversed by fine linear shadows indicating trabeculae within the cyst. A cyst of large size may be misinterpreted as a tension pneumothorax. The hilar shadow is generally elongated and areas of compressed lung may be seen over the diaphragm or in the apex. The intercostal spaces may be widened. Bronchography will demonstrate eventual bronchiectasis.

Treatment of Alveolar Cysts

Emphysematous blebs or bullae come to treatment when they are large enough to give symptoms or when they rupture, causing spontaneous pneumothorax.

The ideal treatment of giant cysts is local excision of the cyst wall, closing the bronchiolar orifices. In some cases only the lung parenchyma adjacent to the cyst need be sacrificed. The lung is re-expanded by suction drainage after the operation. If the cyst is complicated by bronchiectasis, a lobectomy or segmental resection must be performed.

If the blebs or bullae are part of a more generalized emphysema, only the complication of spontaneous pneumothorax is treated. These cases need careful physiologic investigation, including bronchspirometry, arterial oxygen determination, and heart catheterization. The prognosis of the emphysema is not too good, and the patient's respiratory function must not be impaired by the treatment.

Acute spontaneous pneumothorax is treated

by bed rest and adjustment of the pleural pressures to permit a gradual re-expansion of the lung. If the lung fails to expand after the acute attack of spontaneous pneumothorax, this may be due to intrapleural adhesions, to ruptured bronchogenic cysts, to scar tissue in a bronchiole, or to a visceral pleural membrane. When after medical treatment for a short period the lung remains collapsed, more active therapy has to be instituted.

Thoracoscopy is performed for diagnostic purposes; and when stringlike adhesions are present, these are divided with the cautery to relax the tension on the lung and permit rapid healing of the pulmonary rent with re-expansion. Artificial pleurodesis by the introduction of silver nitrate (Brock) or talc powder (Blades) may prevent further pneumothorax, but may also cause a fixation of the diaphragm, with impaired pulmonary function, and is not recommended as a routine procedure.

Open thoracotomy is the procedure of choice. Then a complete pneumolysis is performed, the pulmonary rent is closed, the emphysematous bleb or bulla is resected and, if necessary, a decortication of the lung is performed to allow re-expansion. The resection may be limited to the cyst responsible for the pneumothorax and other peripheral large cysts or bullae that might rupture. An attempt to remove all blebs and bullae will often prove impossible without lobectomy or pneumonectomy. This is usually contraindicated in these frequently bilateral cases, where the conservation of pulmonary tissue is most important.

Treatment of Bronchial Adenomas

J. Maxwell Chamberlain
and
Charles F. Daniels

Bronchial adenoma is the most provocative of the endobronchial tumors. It has been considered both malignant and benign [2, 4, 6, 7]; its microscopic appearance is varied; its clinical picture varies from a tickling cough to a suffocating asthma; and its treatment includes both pneumonectomy and simple bronchoscopic removal. The combined experience of pathologists, physicians, and surgeons is still insufficient for there to be complete unity of attitude on these tumors, but the majority of surgeons who treat them are decidedly in favor of resection therapy whenever it is technically possible.

The combined reported experience of these tumors is about one thousand cases. Until resection therapy was generally accepted, it was difficult to evaluate the pathologic material accurately, since by endoscopic methods the tumor was removed in small pieces rather than en masse.

The typical bronchial adenoma arises within the wall of a major or segmental bronchus. When viewed bronchoscopically, it is covered by bronchial mucosa and only a small part of it may be visible within the lumen. The major portion may be and usually is extrabronchial.

Some confusion exists as to which bronchial neoplasms should be included in the term "bronchial adenoma." Because of the multiplicity of cytologic tumor types that have the same general structure and behavior, it seems convenient to apply the term "bronchial adenoma" to all endobronchial neoplasms that are not frank bronchogenic carcinoma.

If such an all-inclusive classification is made, bronchial adenomas must be considered to be both benign and malignant, although their malignant nature is more potential than actual. The natural history of these tumors is long, compared to that of the common carcinomas; yet they do occasionally metastasize to the regional lymph nodes or to distant organs such as the liver and brain, late in the course of the disease. Because adenomas are rarely found in general autopsy material [22], it has been assumed that in a few cases degeneration occurs or a malignant neoplasm arises in a bronchial adenoma of long standing.

SITES OF ORIGIN OF BRONCHIAL ADENOMAS

The primary sites of these tumors have been well demonstrated by clinical experience and pathologic study. They arise in the trachea, main bronchi, or proximal portions of segmental bronchi. In most instances, some portion of the tumor may be seen at bronchoscopic examination. In a few cases, all the tumor seems to be within the lumen of the tracheobronchial tree, attached by a small pedicle; while in others the tumor has a broad base and protrudes into the lumen for a relatively short distance in comparison to its extrabronchial extension.

MICROSCOPIC HISTOLOGY OF BRONCHIAL ADENOMAS

The bronchi and trachea are composed of a variety of tissues of endodermal and mesenchymal origin: ciliated and cuboidal epithe-

lumen, serous and mucous glands, smooth muscle, cartilage, and fibrous connective tissue. During the development of these structures, blood vessels and nerves grow into the trachea and the bronchi to become an integral

(3) mixed tumors, (4) mesodermal tumors, (5) simple adenomas. Carcinoids, cylindromas, and mixed tumors have been observed to metastasize more commonly than the others.*

The distinguishing characteristics of the bronchial adenoma, then, are its occurrence within a known range of the endobronchial tree, its slow growth, and the fact that its intrabronchial extension may be minimal compared with its total size, and that the regional lymph nodes may be the foci of metastases.

CLINICAL FEATURES OF BRONCHIAL ADENOMAS

A

The incidence of bronchial adenoma as to sex and age differs from that of carcinoma of

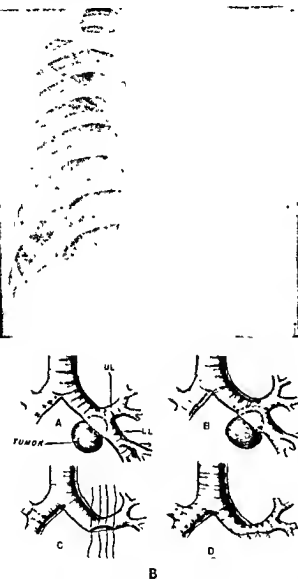


Fig 17-1. a Roentgenogram of the chest showing almost total atelectasis of the left lung due to an adenoma. b. (A) Intrabronchial and extrabronchial components of the bronchial adenoma, (B, C) line of resection for surgical extirpation of the adenoma, (D) closure of the bronchus. c Roentgenogram of the chest twelve years postoperatively

part of the organs. Therefore, it is not surprising to discover a tumor whose cytologic type may have been derived from one or more of these basic tissues [5, 17]

Consideration of the cell types is important from the prognostic point of view. There are five basic common types of bronchial adenomas (1) carcinoids, (2) cylindromas,

* EDITORIAL NOTE Adenomas of the carcinoid variety may produce the typical carcinoid syndrome associated with the release of excessive amounts of serotonin. This syndrome consists of protracted flushes, diarrhea, and cardiac valvulitis. The diagnosis can usually be made by noting an increase of urinary excretion of 5-hydroxy-indoleacetic acid. Reports of the carcinoid syndrome resulting from either a localized bronchial adenoma or from metastases from a bronchial adenoma of the carcinoid type have appeared in the recent literature [15, 16, 19]

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MICROSCOPIC HISTOLOGY OF BRONCHIAL ADENOMAS

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Endoscopic Removal of Pulmonary Adenomas

The hazards of endoscopic removal are hemorrhage, stenosis, and recurrence of the tumor.

slaughters, a fatal hemorrhage may occasionally ensue [9].

Stenosis, moderate to severe, is always present after endoscopic removal of all except the rare pedunculated tumors. A partial

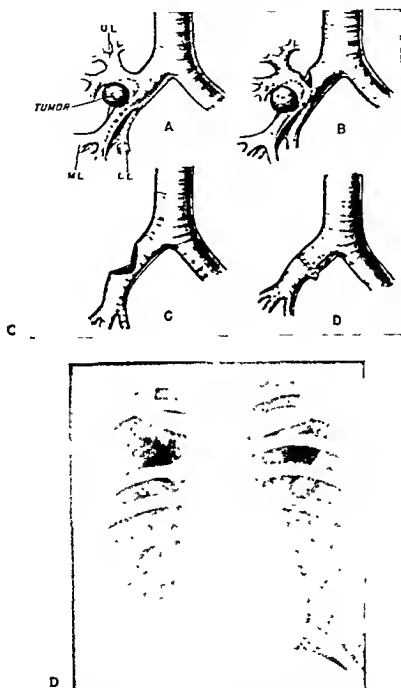


Fig 17.2 (Cont'd) c (A) Intrabronchial and extrabronchial tumor; (B,C) line of excision for surgical removal of the tumor, (D) bronchial closure d Chest x ray eighteen months postoperatively.

Hemorrhage at the time of removal of the adenoma can usually be controlled by modern electrocoagulating instruments, but seven to ten days later, when the cauterized tissue

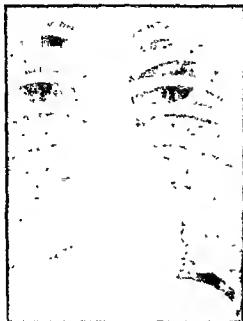
stenosis interferes with ventilation and the cleansing mechanism of the lung distal to the stricture. At the level of the cauterization the ciliated epithelium is lost and bronchial peri-

the lung in that adenomas are slightly more common in women than in men, and are discovered in the third and fourth decades of life.

The symptoms vary from a tickling cough to a fatal hemoptysis, but are usually those of pulmonary suppuration. When the tumor becomes engorged and touches the adjacent or opposite bronchial wall, cough is produced.

tumors of similar size, positive diagnosis is the rule. For this reason, tissue diagnosis is not essential, but bronchoscopic observation is of paramount importance.

Roentgenograms may show the extra-bronchial extension or the result of partial or complete obstruction of the bronchus, but tomography clarifies the intrabronchial and extrabronchial components.



A



B

Fig 17-2. a. Preoperative roentgenogram of the chest showing a bronchial adenoma. b. Tomogram showing intra bronchial and extrabronchial extent of the tumor

This may precipitate severe paroxysms of coughing through change in the size of the bronchial lumen. Occasionally a small ulceration in the mucosa occurs, with a resulting alarming hemorrhage from the vascular zone just beneath the epithelium. These ulcerations have a tendency to heal rapidly. As the tumor enlarges within the lumen, bronchial occlusion and its sequelae occur.

The diagnosis is suggested first by the chronicity of the symptoms, but *bronchoscopy* usually demonstrates a pink, smooth, pedunculated or rounded tumor, which often occurs at bronchial spurs.

Biopsy is often misleading, because the small piece of tissue removed may include only the normal surface epithelium and thickened capsule, without identifying tumor cells. In biopsy of carcinomas, given endobronchial

TREATMENT OF BRONCHIAL ADENOMAS

The literature is replete with instances of ten to twenty years survival with symptoms and no treatment. It is not uncommon for a patient to report a cough of five to six years' duration, complicated by several acute episodes of pulmonary suppuration, before diagnosis is made. Endoscopic excision, lobectomy, and pneumonectomy have produced clinical cures only to have regional or distant metastases make their appearance five to twenty-five years later.

Certain tumors located in the tracheal wall or the tracheal bifurcation may lend themselves to local excision and plastic closure of the bronchus or trachea [21]; in others, it may be necessary to resort to endoscopic methods.

Pulmonary Cancer: An Appraisal

Irving M. Ariel
and
George T. Pack

INCIDENCE OF PULMONARY CANCER

An ancient military adage states that there is a defense for every offense. It is indeed fortunate that a defense is available to combat pulmonary cancer inasmuch as this form of cancer has increased in incidence to an extent that has assumed pandemic significance. No other noninfectious disease has increased at such an alarming rate.

The United States National Office of Vital Statistics reported 2,837 deaths from lung cancer in 1930, which value had increased to 18,313 in 1950. This increment of 500 per cent emphasizes the prevalence of this form of cancer in the United States. Case has reported that 15,615 men and 2,571 women died from lung cancer in England and Wales during 1956. The United Nations (*Demographic Yearbook*) and the World Health Organization (*Annual Epidemiological and Vital Statistics*) have reported a high incidence of lung cancer. A high incidence of deaths from cancer of the respiratory tract in males has been listed for the three-year period 1951-1953 (19): Australia, 0.204; Canada, 0.202; Denmark, 0.236; Finland, 0.419; France, 0.285; Germany (Federal Republic), 0.315; Ireland, 0.215; Israel (Jewish population), 0.112; Italy, 0.164; The Netherlands, 0.306; New Zealand, 0.268; Scotland, 0.572; England and Wales, 0.617; Northern Ireland, 0.279; United States, 0.263*.

Despite the fact that a quarter-century has elapsed since the first successful pneumonectomy was performed for pulmonary cancer, the number of patients who are being cured of this

form of cancer remains disappointingly low. Bignall concludes that of all the lung cancers occurring in patients in England and Wales less than a fourth are resected and more than half of the patients receive neither surgical nor radiation therapy. In the United States, approximately 9 per cent of all patients with pulmonary cancer survive five years or longer. Critical examination of those factors which contribute favorably to and those which conspire against curing a patient with pulmonary cancer is being made. A major finding has been the delay that occurs from the onset of the cancer and the time that the patient is operated upon—a delay reflected by the advanced stage of the neoplasm, permitting resection in less than one fourth of all the patients seen.

DIAGNOSIS OF PULMONARY CANCER

The diagnostic procedures of roentgenographic examination of the chest, bronchoscopic examination, scalene node biopsy, cytologic examination of exfoliated cells, examination of pleural fluid, thoracoscopy, and lung aspiration will yield a positive diagnosis for cancer in a significant number of cases, but usually after the neoplasm has reached an advanced stage.

Attempts to discover asymptomatic lung cancer by mass x-ray survey reveal that of 1,780,178 surveys reported by the Public Health Service from nine different cities in the United States there were 1,382 suspects, or 0.8 per 1,000 persons examined. The actual number of lung cancers is less than the "suspect yield" and averages 0.1 to 0.2 per 1,000. The largest roentgenographic survey

*Death rates per thousand living per year

stasis is reduced by intramural induration and fibrosis. Air movement across the stenosis may not then be normal, and in severe strictures an actual obstructive emphysema may occur. All this means that infection distal to the strictures is assured, which, when repeated several times, leads to destruction of the lung from obstructive emphysema, bronchiectasis, lung abscess, or atelectasis, or from a combination of these.

Recurrence is likely after endoscopic removal because at endoscopy these tumors are only partially visible, the much larger extrabronchial components remaining unseen. Prior to the use of resection therapy, great stamina was exercised by both the patient and the endoscopist in any effort to effect a cure by this means.

Probably the best indication for endoscopic treatment at the present time is the necessity of a temporizing procedure, as when partial resection of the tumor to re-establish bronchial drainage is indicated in order that resection may be carried out more successfully and with less risk at a later date.

Surgical Resection of Bronchial Adenomas

Resection with minimal loss of pulmonary tissue is justifiable for these patients because only a few of the tumors are invasive and the degree of malignancy is very low. The few cases in which there are distant metastases hardly justify the same attitude as is taken toward bronchogenic carcinoma, but, if desirable, it may still be possible to do a mediastinal dissection after a lobectomy.

Often a lobectomy is technically possible even though the tumor is proximal to the upper-lobe orifice. Of course, if the tumor has been present for many years and the lung is completely destroyed beyond the tumor, a pneumonectomy is indicated.

Conservation of the pulmonary tissue is best demonstrated by the following experience in the treatment of a bronchial adenoma. The patient had had intermittent atelectasis of the left lower lobe associated with infection for several years. Finally, total atelectasis of the lung (Figure 17-1a), dyspnea, high

temperature, etc., brought her to bronchoscopy. A bronchial adenoma was seen arising from the medial wall of the left main bronchus opposite the left upper-lobe orifice. At operation a bronchotomy was done, and the lower lobe and part of the medial wall of the left main bronchus was removed with the specimen. A plastic closure of the bronchus was done and the upper lobe preserved (Figure 17-1b). After operation, the left main bronchus would accept a 7-40 bronchoscope as far down as the upper-lobe orifice. The patient was well and working as a bridge toll collector in the twelve years he was followed (Figure 17-1c).

Another example of conservatism is demonstrated by a twenty-two-year-old girl who had paroxysmal coughing attacks that led to bronchoscopy in the face of an almost normal chest film (Figure 17-2a). Tomography localized the intrabronchial and extrabronchial components (Figure 17-2b). The adenoma was found distal to the upper-lobe orifice, concealing the middle-lobe orifice but involving the inferior wall of the upper-lobe bronchus. At operation, the upper and middle lobes were removed, but the medial wall of the intermediate bronchus was preserved and a plastic closure done by bringing the lower-lobe bronchus up to the right main-stem bronchus (Figure 17-2c). This patient is well, eighteen months after resection, and living a normal life (Figure 17-2d). A pneumonectomy followed by thoracoplasty would have been a much greater price for a young, unmarried woman to pay in terms of the sacrifice of lung tissue and deformity. (See Chap. 22A for a presentation of the anatomy and surgical considerations of segmental pulmonary resection in treating lung tumors.)

Radon seeds and x-ray therapy in the management of these cases are mentioned only to be condemned. Even the tracheal tumors allow of localized excision with plastic repair, which is a better solution. A slight reduction in the diameter of the lumen, should it occur after removal of a tracheal tumor, is preferable to a stricture with the tumor still present and capable of recurring. (See Chap. 15 for a discussion of the treatment of tracheal tumors.)

TABLE 18-1.—SURVIVAL OF PATIENTS WITH UNTREATED PULMONARY CANCER

Author	Number of patients	Survival in months
A FROM TIME OF FIRST SYMPTOM UNTIL DEATH		
Fulton (1936)	915	7.6
Steiner (1940)	53	10.5
Tenzel (1941)	121	10
Tinney (1944)	315	14.5
Ariel <i>et al</i> (1950)	340	9.4
Wiklund (1951)	66	13
B FROM TIME OF DIAGNOSIS UNTIL DEATH		
Chandler and Potter (1927)	67	6
Vinson (1936) (reviewed by Leddy, 1943)	30	6
Overholt (1940)	26	8
Farberov and Baslow (1941)	21	6.5
Tinney (1944)	315	6
Hilton (1945)	51	2.5

specific treatment, stated that death occurred an average of 9.4 months after the onset of symptoms.

From the time of diagnosis until death the average survival time varied from ten weeks (Hilton, 51 patients) to about six months (Tinney, 315 patients, Chandler and Potter, 67 patients; Farberov and Baslow, 21 patients) to eight months (Overholt).

Of Widmann's series of 119 untreated patients with bronchogenic carcinoma, 94 per cent were dead within six months and not a single patient lived longer than one year. A similar situation obtained for 125 untreated patients reported on by Leddy.

Occasional reports have appeared in the literature of patients who have lived for prolonged periods with untreated bronchogenic carcinoma.

DELAY IN THE DIAGNOSIS OF PULMONARY CANCER

From the above values, of death occurring about one year after the onset of symptoms and within six months after the diagnosis has been established in patients with untreated bronchogenic carcinoma, it may be assumed that a delay of six months generally occurs from the onset of symptoms until the diagnosis is made. This has been the reported experience. Tinney reported an average delay

from the onset of symptoms until diagnosis of 8.5 months. In 1,205 patients reported on by Ariel and his associates [3], the delay from the onset of symptoms until admission to the hospital was 7.3 months. Björk [8] evaluated the causes for delay and observed that a total delay of 8.4 months occurred from the onset of symptoms until definitive therapy was instituted in his large series of patients reported from the Brompton Hospital in England; the average delay due to the patient was 3.4 months and the delay due to the doctor was five months. Overholt has remarked that most patients do not seek medical attention until three to four months after the onset of symptoms, but that in 50 per cent of the cases the physician does not make a diagnosis for six months or longer after the patient seeks medical aid.

It is impossible to judge accurately the duration of a given cancer because some patients are stoical and are not cognizant of mild symptoms, and certain cancers can remain occult in a silent pulmonic zone and not produce symptoms until late in their course. Not infrequently, symptoms resulting from distant metastases may herald the presence of a cryptic bronchogenic carcinoma.

Rigler, O'Loughlin, and Tucker [65] interpreted the duration of bronchogenic carcinoma from previous roentgenographic data. They found that the average duration of symptoms in 37 patients with inoperable lung cancer was 12.7 months and that roentgenographic signs preceded the onset of symptoms by 7.8 months; that the average duration of cancer in 13 operable patients, as evidenced roentgenographically, was 36.4 months. Roentgenographic examination is unquestionably a more accurate index of the duration of pulmonary cancer than are the patient's symptoms, but frequently the early roentgenograms are interpreted correctly only in retrospect.

SURGICAL TREATMENT OF PULMONARY CANCER

OPERABILITY RATE

Inasmuch as surgical resection is the only method of curing cancer of the lung, the accomplishments of this procedure are an-

was reported by Guiss in 1950 from Los Angeles County; in this, 1,867,201 chest minifilms were made and 222 instances of bronchogenic carcinoma were discovered (0.12 per 1,000) [38]. The inadequacy of minifilm chest survey is revealed by the fact that in 1950 in Los Angeles County there were 27 deaths from lung cancer in individuals with negative minifilms; in 1951 there were 133 deaths and in 1952, 146 deaths in individuals with normal chest roentgenograms in 1950. These data demonstrate the need for repeat roentgenographic surveys and the fact that a negative report does not exclude the presence of cancer but may give the individual a false sense of security.

The survival rate of patients who are asymptomatic and whose cancers are diagnosed in the course of a roentgenographic survey is better than the over-all survival. Churchill, Sweet, Scannell, and Wilkins reported [23] the cumulative five-year survival for thirty-eight "survey" patients operated upon in the years 1948-1956 to be 42 per cent, in contrast to a five-year survival of 28 per cent for all resections (220) performed during the same period. Overholt reported that of twenty-nine survey patients seen over five years ago, 24 per cent are alive and well.

A solitary, discrete lung shadow was the sole finding in over 57 per cent of patients reported on by Overholt, who emphasizes the need for an exploratory thoracotomy in any patient with a discrete lung shadow, even in the absence of symptoms.

In this connection, Cahan's study of patients known to have cancer elsewhere in the body or who have been treated for cancer and reveal a solitary lung shadow is of note. He showed that of 208 instances of solitary lung shadow in patients with primary cancers elsewhere, 162 were found to be another primary cancer and in only 46 cases (22 per cent) was the shadow caused by a metastasis. He concludes, as "a good rule of thumb" [18]:

If the patient has a squamous carcinoma elsewhere in the body, the lung lesion is usually a separate primary and predominantly a squamous carcinoma as well.

If the patient has a soft part or skeletal sarcoma or melanoma elsewhere, the solitary lung lesion is almost always a metastasis from these.

If there is an adenocarcinoma elsewhere, there

is about a 50 per cent chance of the solitary shadow being a primary lung cancer.

Figure 18-1 shows the sites of 141 multiple primary tumors, one of which was in the lung, in Cahan's study. He stresses an attitude of aggression in such cases, including "resection of the pulmonary lesion with as much of the local lymphatics as possible. In this ambiguous setting, if the lesion is peripheral a radical lobectomy is used; if it in-

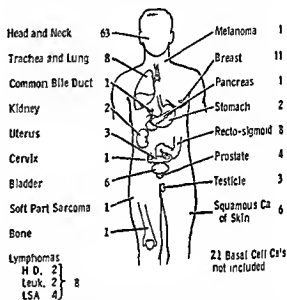


Fig 18-1 Sites of 141 multiple primary cancers from Memorial Center. One of these was in the lung. 21 basal-cell carcinomas are not shown (From W. G. Cahan [18], courtesy Medical Science.)

involves the main bronchus or is too large for a lobectomy, a radical pneumonectomy is performed." (Chap 22B.)

THE COURSE OF PATIENTS WITH UNTREATED PULMONARY CANCER

As a base line for evaluating the accomplishments of the attack upon lung cancer, the probable course of a patient bearing bronchogenic carcinoma who received no treatment whatsoever is examined (Table 18-1). The average duration of life of 1,810 untreated patients reported by different authors, from the time of the first symptom, was 10.8 months. Fulton reviewed the records of 915 such patients and found the average duration of life to be 7.6 months. Ariel, Avery, Kanter, Head, and Langston [3], reporting on 340 patients with pulmonary cancer who received no

TABLE 18-3.—RESECTABILITY AND SURVIVAL RATES FOR 4,814 PATIENTS WITH PULMONARY CANCER

<i>Senior author and year</i>	<i>Number of cases</i>	<i>Explored Per cent</i>	<i>Resected Per cent</i>	<i>5-year survivals Per cent</i>
Gibbon (1953)	532	71	39	9
Ochsner (1954)	1,170	52	33	8
Kirklin (1955)	767	48	24	8
Overholt (1956)	733	62	37	8
Burford (1958)	1,008	60	35	9
Churchill (1958)	604	55	35	10
Total	4,814	58	34	8.6

incidence of 18.2 per cent (collective series). Their data include patients from the earliest days of thoracic surgery. Recent reports from six large clinics in the United States reveal an average resectability rate of 34 per cent for 4,814 patients (Table 18-3; Figure 18-2).

The percentage of patients who have been subjected to a thoracotomy and in whom resection can be performed varies widely, depending upon the criteria for performing a thoracotomy (Table 18-4).

TABLE 18-4.—PERCENTAGE OF THORACOTOMIZED PATIENTS WITH PULMONARY CANCER IN WHOM A RESECTION COULD BE PERFORMED

<i>Author and year</i>	<i>Number of patients</i>	<i>Per cent in whom resection performed</i>
Brock (1943)	33	45
Brindley (1944)	90	50
Rienhoff (1944)	181	39
Bjork (1947)	152	49
Churchill (1948)		
(from the literature)	782	58
Churchill <i>et al.</i> (1950)	294	58
Moore (1951)	155	56
Bloomer and Lindskog (1951)	120	52
Ochsner <i>et al.</i> (1952)	750	65
Borrie (1952)	810	42
Gibbon <i>et al.</i> (1953)	380	54
Aufses (1953)	330	50
Brea (1954)	311	64
Abbey Smith (1957)	147	98
Overholt and Bougas (1957)	457	57
Rienhoff <i>et al.</i> (1958)	699	36
Churchill <i>et al.</i> (1958)	330	64
Johnson <i>et al.</i> (1958)	192	60
Burford <i>et al.</i> (1958)	605	58
Ochsner (1958)	759	62
Kirklin <i>et al.</i> (1958)	369	50
Bignall (1958)	527	75

OPERATIVE MORTALITY RATE

The hospital mortality rate incident to the operative procedure for bronchogenic cancer has been rather high in past years. These values are listed in Table 18-5, and vary from

TABLE 18-5.—OPERATIVE MORTALITY FOLLOWING SURGICAL TREATMENT OF PULMONARY CANCER

<i>Author and year</i>	<i>Number of patients operated upon</i>	<i>Operative mortality Per cent</i>
Brock (1943)	32	28
Brindley (1944)	45	32
Rienhoff (1944)	71	21
Edwards (1946)	70	17
Sellors <i>et al.</i> (1947)	122	15
Bjork (1947)	81	30
Rienhoff (1947)	112	22
Gagnon (1948)	44	36
Mason (1949)	202	27
Overholt (1949)	45	11
Churchill <i>et al.</i> (1950)	171	20
Graham (1950)	75	30
Taylor and Waterhouse 1950 (culled from England)	1,239	24.3
Brown <i>et al.</i> (1951)	34	5.9
Wiklund (1951)	73	20
Ochsner <i>et al.</i> (1952)	332	20
Borrie (1952)	128	22
Brea (1954)	200	18
Bignall and Moon (1955)	531	15
Kirklin <i>et al.</i> (1955)	184	13.6
Watson (1956)	167	12.3
Abbey Smith (1957)	147	12
Gibbon and Nealon (1957)	145	23
Cleland (1958)	599	13
Churchill <i>et al.</i> (1958)	127	10
Johnson <i>et al.</i> (1958)	116	7.7
Burford <i>et al.</i> (1958)	603	11
Ochsner (1958)	759	20
Rienhoff <i>et al.</i> (1958)	699	22

TABLE 18-2.—OPERABILITY OF PATIENTS BEARING PULMONARY CANCER*

Author and year	Number	
	of patients	operated upon Per cent
Neuhof <i>et al.</i> (1942)	281	11
Brindley (1944)	448	10
Lindskog (1946)	100	34
Rienhoff (1947)	327	34
Jones (1947)	196	20
Graham (1949)	260	22.3
Ariel <i>et al.</i> (1950)	1,057	13.4
Churchill <i>et al.</i> (1950)	1,130	26
Moore (1951)	370	42
Bloomer and Lindskog (1951)	300	40
Borrie (1952)	1,800	45
Aufses (1953)	959	35
Brea (1954)	880	35
Kirklin <i>et al.</i> (1955)	767	48
Overholt and Bougas (1957)	733	62
Bignall (1958)	1,749	29
Churchill <i>et al.</i> (1958)	604	55
Johnson <i>et al.</i> (1958)	344	56
Burford <i>et al.</i> (1958)	1,008	60
Ochsner (1958)	1,453	52
Total	14,766	34.9

* Patients considered candidates for surgical intervention of their lung cancer. In many instances, only exploratory thoracotomy performed.

alyzed. The percentage of all patients bearing pulmonary cancer on whom a surgical attack may be attempted is disappointingly low. Rosenblatt and Lisa [66], in a review of almost fifteen thousand cases, found that less than 35 per cent of the lung cancers were

considered operable. In a separate review of 14,766 cases, the present authors record a similar average operability rate (34.9 per cent) (Table 18-2). The operability rate varies from 10 per cent (Brindley [12]) to 62 per cent (Overholt and Bougas). The lower operability rates are significant in view of the relatively few contraindications to surgery, the major one being evidence of metastasis. Table 18-2, arranged chronologically, reveals a progressive increment in the percentage of patients who are candidates for the surgical removal of lung cancers. Thus, Lindskog [45] reported from Yale University an operability rate of 34 per cent, which increased to 40 per cent in 1951. Graham [35] reported from Barnes Hospital (St. Louis) an operability rate of 22.3 per cent, which rose to the high value of 60 per cent in the same institution as reported by Burford and his associates in 1958. The operability can fluctuate widely in different institutions, depending upon such factors as preadmission selection, the policy of the institution (palliative versus only curative type of surgery), the temperament of the surgeon, and other variables.

RESECTABILITY RATE

Approximately one fifth of all patients with pulmonary cancer can have the benefit of a chance for cure by surgical measures. Rosenblatt and Lisa [66] record 2,697 resections in 14,795 patients with bronchogenic cancer, an

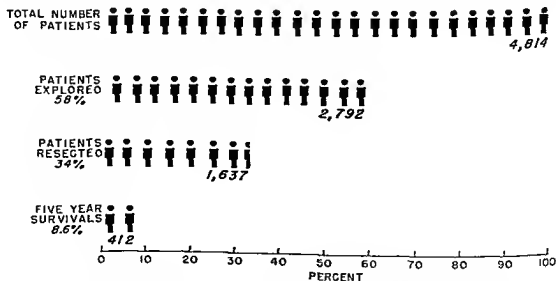


Fig. 18.2. Resectability and survival rates for patients with cancer of the lung

TABLE 18-3.—RESECTABILITY AND SURVIVAL RATES FOR 4,814 PATIENTS WITH PULMONARY CANCER

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incidence of 18.2 per cent (collective series). Their data include patients from the earliest days of thoracic surgery. Recent reports from six large clinics in the United States reveal an average resectability rate of 34 per cent for 4,814 patients (Table 18-3; Figure 18-2).

The percentage of patients who have been subjected to a thoracotomy and in whom resection can be performed varies widely, depending upon the criteria for performing a thoracotomy (Table 18-4).

TABLE 18-4.—PERCENTAGE OF THORACOTOMIZED PATIENTS WITH PULMONARY CANCER IN WHOM A RESECTION COULD BE PERFORMED

<i>Author and year</i>	<i>Number of patients</i>	<i>Per cent in whom resection performed</i>
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Björk (1947)	152	49
Churchill (1948)		
(from the literature)	782	58
Churchill <i>et al.</i> (1950)	294	58
Moore (1951)	155	56
Bloomer and Lindskog (1951)	120	52
Ochsner <i>et al.</i> (1952)	750	65
Borrie (1952)	810	42
Gibbon <i>et al.</i> (1953)	380	54
Aufses (1953)	330	50
Brea (1954)	311	64
Abbey Smith (1957)	147	98
Overholt and Bougas (1957)	457	57
Rienhoff <i>et al.</i> (1958)	699	36
Churchill <i>et al.</i> (1958)	330	64
Johnson <i>et al.</i> (1958)	192	60
Burford <i>et al.</i> (1958)	605	58
Ochsner (1958)	759	62
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Bignall (1958)	527	75

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<i>Author and year</i>	<i>Number of patients operated upon</i>	<i>Operative mortality Per cent</i>
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Brindley (1944)	45	32
Rienhoff (1944)	71	21
Edwards (1946)	70	17
Sellers <i>et al.</i> (1947)	122	15
Björk (1947)	81	30
Rienhoff (1947)	112	22
Gagnon (1948)	44	36
Mason (1949)	202	27
Overholt (1949)	45	11
Churchill <i>et al.</i> (1950)	171	20
Graham (1950)	75	30
Taylor and Waterhouse 1950 (culled from England)	1,239	24.3
Brown <i>et al.</i> (1951)	34	5.9
Walland (1951)	73	20
Ochsner <i>et al.</i> (1952)	332	20
Borrie (1952)	128	22
Brea (1954)	200	18
Bignall and Moon (1955)	531	15
Kirklin <i>et al.</i> (1955)	184	13.6
Watson (1956)	167	12.3
Abbey Smith (1957)	147	12
Gibbon and Nealon (1957)	145	23
Cleland (1958)	599	13
Churchill <i>et al.</i> (1958)	127	10
Johnson <i>et al.</i> (1958)	116	7.7
Burlord <i>et al.</i> (1958)	603	11
Ochsner (1958)	759	20
Rienhoff <i>et al.</i> (1958)	699	22

a 5.9 per cent mortality rate for 34 cases, recorded by Brown, Riddle, and Sullivan [16], to a 24.3 per cent mortality rate for 1,239 cases culled from the various hospitals in England. Table 18-5 includes patients treated during the early years of pneumonectomy. The most recent data indicate a continued decrease in the operative mortality for patients subjected to conventional surgical procedures.

When series of cases at a given thoracic clinic are analyzed as regards operative mortality, a steady decrease is noted. Table 18-6 shows the operative mortality for 1,100

TABLE 18-6.—OPERATIVE MORTALITY IN PULMONARY CARCINOMA*
(Overholt Thoracic Clinic Series)

Years	Exploration only Per cent	Resection of localized lesions Per cent
1933-1940	28	33
1941-1945	12	7.7
1946-1950	8.5	13
1951-1953	1.3	2.7

*From R. H. Overholt and J. A. Bougas [53],
courtesy American Journal of Surgery

histologically verified cases treated at the Overholt Thoracic Clinic (Boston). The 28 per cent mortality for simple exploration and the 33 per cent mortality for resection of localized lesions, recorded during the years 1933-1940, dropped precipitously to 1.3 per cent and 2.7 per cent, respectively, for the period 1951-1953.

At the Massachusetts General Hospital the operative mortality for 1948-1956 was 10 per cent for 127 pneumonectomies and 6.4 per cent for 93 lobectomies.

The operative mortality will, of course, vary widely depending upon the selection of patients for operation, the age of the patients (with the higher mortality occurring in the older groups), the willingness of the surgeon to operate in the presence of other concomitant disease processes, and the extent of his resection. The over-all average operative mortality for thoracotomy in patients who are good surgical risks has been reported to be between 1 and 2 per cent—a risk far less than that incident to a watch-and-wait policy in the presence of discrete pulmonary shadows

in asymptomatic patients. The operative mortality tends to increase with the extended radicalness of a given surgical procedure. A mortality of about 3 per cent is recorded for segmental resection; of about 6 per cent for lobectomy; of about 10 per cent for pneumonectomy, and a proportionally higher rate for more extensive resections, including so-called radical pneumonectomy (Watson, 13.6 per cent), resection of the pericardium or chest wall, etc.

SURVIVAL RATE

If a patient bearing pulmonary cancer is fortunate enough to recover from an ablative surgical attack upon the cancer, the chance of five-year survival is good in comparison with the results obtained for other forms of cancer. Approximately one fourth of all patients who are candidates for surgical resection of their lung cancers will survive five years or longer.

Various reports demonstrate a marked variability in the over-all survival rate (Table 18-7). Overholt and Bougas collected data from seventeen sources—6,000 cases of clinically diagnosed lung cancer—for evaluation of five-year survival rates, most of these patients were observed between 1942 and 1950; four fifths had histologic verification. Of 5,704 patients with complete follow-up study, 299 (5.3 per cent) survived five years or more, of this group of survivors, 15 per cent had a localized cancer, 5 per cent had metastases to regional lymph nodes, and 0.3 per cent had distant metastases.

FACTORS THAT INFLUENCE PROGNOSIS

Numerous variables contribute to the prognosis of a given patient bearing pulmonary cancer. These may be analyzed according to (1) the status of the tumor, (2) the general condition of the patient, (3) the skill and experience of the physician caring for the patient.

It is difficult to analyze series of cases from different clinics because of differences in methods of classifying the various neoplasms, differences in philosophy pertaining to indications for operation, and other factors. The dates of the series being analyzed are important inasmuch as prior to 1940 the mortality rate for pneumonectomy was ex-

TABLE 18-7.—FIVE-YEAR SURVIVAL OF PATIENTS WITH PULMONARY CANCER FOLLOWING RESECTION OF THE CANCER

Senior author	Period of study	Resection*		Pneumonectomy		Lobectomy	
		Number of patients	Survival Per cent	Number of patients	Survival Per cent	Number of patients	Survival Per cent
Churchill†	1930-1950	88	27	127	24	93	33
	1950-1957	201	30				
Overholt	1932-1951	261	21	203	7.5		
Rienhoff	1933-1956						
Ochsner	1935-1951	315	15	33	15	16	12
Ariel	1937-1947						
Moore	1939-1949	87	13	99	26	17‡	35
Johnson	1939-1953						
Cleland†	1940-1955	521	27				
Sellers	1940-1950	446	21				
Kirklin	1943-1949	184	37				
Brea	1946-1950	78	9				
Gibbon	1946-1953	205	22				
Burford	1948-1952	182	22				
Bignall§	1951-1955	63	32				

* Extent of resection not given but usually indicates standard pneumonectomy

† Based on patients who survived operation

‡ Recorded as less than pneumonectomy

§ Computed from time of admission to hospital

exceptionally high, which rate has steadily decreased since. Accordingly, any series recorded prior to 1940 would be influenced by the high mortality rate.

The classifications as to the histologic type and grading of neoplasms utilized by different clinics play an important role in the analysis of cases. For example, if bronchial adenoma, which usually carries a survival rate of about 85 per cent, is included with the more malignant tumors, the figures for salvage would be distorted.

The philosophy of the surgeons of a given institution would influence the final outcome. For example: an unusually high resectability rate for a given institution could mean either a critical preadmission scanning of patients, with a resultant increased number of early cancers, or an increased radical approach in which the surgeons are attempting to resect neoplasms that have spread to extrapneumonic structures.

INFLUENCE OF SEX AND AGE ON PROGNOSIS

It is difficult to analyze the effect of sex upon survival because the available data on the survival of women with pulmonary cancer are meager. There was no difference in survival between the sexes in the series reported from the Brompton and Royal Marsden Hospitals in London. Ochsner reported a somewhat better prognosis for women. The ratio of males to females of all his patients with lung cancer was 8:2, whereas the ratio of those patients who survived five years or longer was 4:8, indicating a better survival rate for females.

Regarding the effect of age, there appears to be an improvement in the survival rates with increasing age. Whether this represents a true state of affairs or whether it is a result of reluctance to subject the older patients to resection cannot be stated. Ochsner reported that of all patients subjected to resection who

survived five years or longer only 38 per cent were under fifty years of age, in contrast to 62 per cent who were between fifty and seventy years. Neuman, Ellis, and McDonald, of the Mayo Clinic [52], reported that the operability and resectability rates did not differ in patients under forty years of age, but that the survival rate of this group was much lower. Of 51 patients under forty years of age in their series, only nine had curative resections and none of these lived five years. This is in sharp contrast to the 37 per cent five-year

carcinoma, and undifferentiated carcinoma. The squamous or epidermoid carcinoma is the most frequent form. Rosenblatt and Lisa [66] state that 55 per cent of 203 patients with bronchogenic carcinoma (both autopsy and resected specimens) had squamous carcinomas, 20 per cent adenocarcinomas, and 23 per cent undifferentiated carcinomas. Overholt and Bougas reported on 486 cancers of the lung, of which 60 per cent were squamous carcinomas, 27 per cent adenocarcinomas, and 13 per cent undifferentiated carcinomas

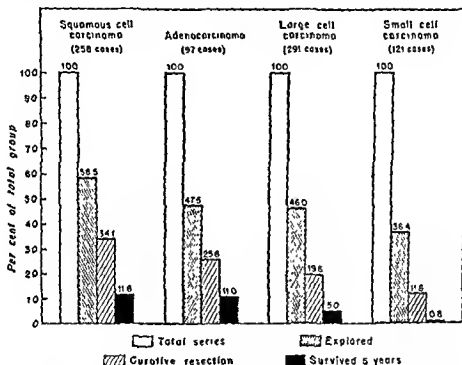


Fig. 18-3 Graphic representation of operability, resectability, and survival rates for the four types of bronchogenic carcinoma (From J. W. Kirklin, J. R. McDonald, O. T. Clagett, H. J. Moersch, and R. P. Gage [42], courtesy Surgery, Gynecology and Obstetrics.)

survival of all patients with bronchogenic carcinoma subjected to a curative procedure by the Mayo Clinic surgeons, as reported by Kirklin, McDonald, Clagett, Moersch, and Gage [42].

INFLUENCE OF HISTOLOGIC TYPE OF TUMOR ON PROGNOSIS

The tendency of different pathologists to classify the neoplasms according to individual dictates influences somewhat the operative results from different clinics. Certain trends, however, are manifest.

The three most common types of lung cancers are squamous-cell carcinoma, adeno-

It is fortunate that squamous carcinoma is the most frequent type inasmuch as most cures have been obtained for this form of lung cancer.

Cleland reported a 42 per cent five-year survival of 118 patients with squamous carcinoma; a 39 per cent survival of 18 patients with adenocarcinoma; and a 22 per cent survival of 74 patients with undifferentiated carcinoma. Of 55 patients who survived five years or longer who were reported on by Overholt and Bougas, 69 per cent had squamous carcinoma, 16 per cent adenocarcinoma, and 15 per cent undifferentiated carcinoma. Burford, Ferguson, and Spjut [17] reported

that 31 of 40 patients (78 per cent) who survived five years or longer had squamous carcinoma, and 12.5 per cent had undifferentiated carcinoma. Ochsner reported that 68 per cent of his patients who survived five years or longer revealed squamous carcinoma, and 8 per cent had adenocarcinoma.

Kirklin and his associates [42] reviewed 844 proved and restudied cases of cancer of the lung to determine the influence of cell type on prognosis. Their findings are recorded in Figure 18-3, and reflect the findings of others, namely, that the best results are obtained for the group bearing squamous-cell carcinoma.

Although the incidence of cures for patients bearing adenocarcinomas and undifferentiated carcinomas is low, it is encouraging that some patients with these forms of cancer are being cured, inasmuch as many present evidence of lymph node and blood vessel invasion by their cancers.

INFLUENCE OF METASTASES TO REGIONAL LYMPH NODES ON PROGNOSIS

When metastases to regional lymph nodes have occurred, the prognosis is poorer than if the cancer remains localized, but it is not necessarily ominous. The incidence of metastases to lymph nodes in patients subjected to resection of their pulmonary cancer is high. It is difficult to assess the true incidence of metastases to the regional nodes because many surgeons make this determination simply on the basis of palpation or a frozen-section examination of a single mediastinal or hilar lymph node. Moreover, unless a "radical pneumonectomy" is performed, the mediastinal and hilar lymph nodes are not removed; and even when they are surgically

excised, painstaking examination by the pathologist, using the clearing technic, is necessary to determine the actual presence of metastases to regional lymph nodes.

Table 18-8 indicates that even when the regional lymph nodes bear metastases from the pulmonary cancer the patient can be cured in a significant number of instances. The survival rates, of course, are higher in those patients who do not have evidence of metastasis to lymph nodes. Overholt and Bougas, in their personal series of patients operated upon between 1932 and 1951, reported a 34 per cent five-year survival rate for 102 patients without evidence of metastases to regional lymph nodes, the survival rate decreasing to 24 per cent of 66 patients who did have lymph node involvement. Metastasis to regional lymph nodes was not as poor a prognostic sign as gross extension of the tumor, in which event only a 4 per cent survival rate was achieved for 93 patients. Johnson, Kirby, and Blakemore [40] reported a 43 per cent five-year survival of 54 patients whose resected lungs did not reveal evidence of metastasis to lymph nodes, in contrast to a 15 per cent survival of 53 patients with evidence of lymph node involvement. Churchill reported a 34 per cent five-year survival rate when metastases to lymph nodes had not occurred; but when the tumor had spread to the regional nodes, no patient survived the five-year span.

INFLUENCE OF BLOOD VESSEL INVASION ON PROGNOSIS

The blood vessels are invaded by pulmonary cancer in a high percentage of patients. Seley reported evidence of blood vessel invasion in 100 per cent of patients with adenocarcinoma.

TABLE 18-8.—FIVE-YEAR SURVIVAL OF PATIENTS WITH METASTASES TO LYMPH NODES FROM PULMONARY CANCER

Author	Number of patients who survived 5 years	With metastases to lymph nodes	
		Number of patients	Per cent
Burford <i>et al.</i>	40	18	45
Overholt and Bougas (collected series)	299	15	5
Overholt and Bougas (personal series)	66	16	24
Johnson <i>et al.</i>	53	8	15

Johnson, Kirby, and Blakemore [40] found evidence of blood vessel invasion in 81 per cent of patients with adenocarcinoma and in 100 per cent of patients with undifferentiated carcinoma. Langston, Laws, McGrew, Heidenreich, and Slominski [43] found evidence of vascular invasion in fourteen of fifteen patients with pulmonary cancer after resection either by lobectomy or pneumonectomy; four of these neoplasms were anaplastic carcinomas, the remainder were squamous-cell carcinomas. Collier, Blakemore, Kyle, Enterline, Kirby, and Johnson [26] found evidence of blood vessel invasion in 71 per cent of pulmonary tumors (undifferentiated carcinoma, 100 per cent; epidermoid carcinoma, 63 per cent; bronchiolar carcinoma, 45 per cent; adenoma, 12 per cent).

In this connection, Moore, Sandberg, and Schulbarg [49] analyzed the blood of patients with pulmonary cancer for the presence of cancer cells and demonstrated that 75 per cent of the patients had cancer cells in their peripheral blood.

Although blood vessel invasion is an ominous sign, five-year survivals of some patients who have evidenced this method of spread have been reported. Overholt and Bougas [58] in a review of the literature, reported that 0.3 per cent of 299 patients who survived five years or longer after resection of their pulmonary neoplasm presented evidence of distant metastases, presumably via the route of blood vessel dissemination. Johnson and his associates [40] stated that of 71 patients with blood vessel invasion, only 6 per cent survived five years or longer, whereas

of 36 patients without evidence of such invasion, 75 per cent survived five years or more. They analyzed the relative effect upon prognosis of cancerous invasion of blood vessels and/or metastases to lymph nodes in their series of patients (Table 18-9).

Metastasis of bronchogenic cancer to the adrenal glands, which occurs in a significant number of patients, does not necessarily indicate that dissemination has occurred by way of the blood stream. Dr. Kenneth Meyer [48] has demonstrated that there are definite lymphatic connections between the lower lobes of both lungs and the lymphatics below the diaphragm, to the adrenal gland.

OTHER FACTORS THAT INFLUENCE PROGNOSIS

Other factors that have been studied in an effort to assess the prognosis of pulmonary cancer include the location of the tumor, the size of the tumor, the delay before diagnosis, and the type of treatment.

TREATMENT OF PULMONARY CANCER

The majority of cures have been obtained by surgical resection of the pulmonary cancer. An occasional patient will survive five years or longer without any treatment. Overholt and Bougas reported a 2 per cent five-year survival of 131 patients gleaned from the literature who were subjected to radiation therapy. Leddy and Moersch [44] reported on 125 patients treated by irradiation, of whom 4 per cent lived five years or longer. (Chapters 25, 26, and 27 discuss in detail the radiation treatment of pulmonary cancer.)

TABLE 18-9—CARCINOMA OF THE LUNG—FIVE-YEAR SURVIVAL OF 107 PATIENTS SURVIVING RESECTION*

	Blood vessel invasion	Lymph node invasion	Resected	Alive 5 years	Per cent
1.	+		71	4	6
2.	—		36	27	75
3.		+	53	8	15
4.		—	54	23	43
5.	+	—	28	2	7
6.	+	+	24	2	8
7.	—	+	10	6	60
8.	—	—	26	21	81

* SOURCE: J. Johnson, C. K. Kirby, and W. S. Blakemore [40], courtesy *The Journal of Thoracic Surgery*.

RADICAL RESECTIONS

Standard pneumonectomy is the operation most frequently performed for pulmonary cancer. With the decline in the operative mortality for standard pneumonectomy, efforts have been put forth in three directions, namely, to increase the resectability rate of lung cancer, to offer palliation to patients whose cancers are found to be inoperable at the time of thoracotomy, and to modify the operative procedure in a more conservative direction for those patients whose general condition or pulmonary reserve will not tolerate a standard pneumonectomy.

At the present time there are at least seven different procedures available for surgically treating the patient with pulmonary cancer. These include: segmental resection; simple lobectomy; radical lobectomy; standard pneumonectomy; radical pneumonectomy (pneumonectomy combined with resection of hilar and mediastinal lymph nodes); pneumonectomy combined with resection of contiguous structures such as chest wall, diaphragm, etc., and exploratory thoracotomy with interstitial irradiation.

In certain instances, the type of operation, e.g., resection of the lung and contiguous structures or the interstitial irradiation of the exposed cancer, will be dictated by the extent of the cancer. In other instances the pulmonary reserve of the patient will dictate a more conservative operative procedure.

The exact status of the various operative procedures is being evaluated. Individual thoracic surgeons have personal convictions regarding the indications for and accomplishments of the various procedures. Weinberg (Chap 19), on the basis of studies of the distribution of the hilar and mediastinal lymph nodes, favors the radical pneumonectomy. Allison [2] and Brock and Whytehead [14] also favor the radical pneumonectomy, with isolation and division of the pulmonary vessels within the pericardium to increase the margin between the tumor and the line of resection. Watson [74] reported a mortality rate of 13.6 per cent for 125 radical pneumonectomies. He also reported a 27 per cent five-year survival rate for 74 patients subjected to radical pneumonectomy, which value, obtained for selected patients, is not significantly

better than the 23 per cent five-year survival obtained for 26 patients subjected to standard pneumonectomy.

Johnson, Kirby, and Blakemore [40] compared the accomplishments of radical pneumonectomy with their results obtained by standard pneumonectomy in 116 patients, and call attention to the fact that their five-year survival rate of 26.7 per cent equals the results obtained by radical pneumonectomy. They state that until it can be shown that radical pneumonectomy produces superior results, the surgeon is not obliged to perform the radical operation, and voice their plan to continue to perform the standard pneumonectomy except in instances where extension of the procedure is indicated in order to resect gross neoplasm.

When the cancer has spread beyond the confines of the lung to involve chest wall or bronchus, the prognosis is poor. Overholt and Bougas reported a 4 per cent five-year survival of 93 patients who had gross extension of their cancers. Kirklin and his associates [42] reported one patient living and well five years after resection of the chest wall and lung for pulmonary cancer; they advise a continuation of resecting contiguous structures where technically possible.

In the case of the Pancoast syndrome, the upper lobe, with the upper ribs and chest wall and part of the brachial plexus, can be resected [21, 28]. Vareo [72] combined a fore-quarter amputation with pneumonectomy for the Pancoast syndrome, retaining the scapula, which was used to close the operative defect. His patient, however, developed paradoxical respiration and respiratory acidosis, and succumbed.

CONSERVATIVE RESECTIONS

In contrast to the aggressive approach, Maier [46] favors a conservative attitude and has stated that "the little that can be gained by a very radical approach is more than offset by the higher morbidity and mortality, especially in those cancers with a very low surgical salvage potential, such as the oat-cell type."

Efforts are being made to assess the accomplishments of the more conservative surgical procedures. Lobectomy has been utilized

by thoracic surgeons for treating certain pulmonary cancers, and the reported results seem to indicate that the chances for prolonged survival are not significantly lessened by this more conservative procedure (see Chap. 22A). In an effort to combine lobectomy (with the preservation of normal lung tissue) and resection of the lymph nodes draining the lobe, Cahan has developed the "radical lobectomy," in which the involved lobe, the intervening lymphatics, and the lymph nodes to which metastases can spread are resected (see Chap. 22B).

It is impossible to compare the reported results of the different operative procedures. For example, lobectomies are usually performed in patients with small peripheral tumors, whereas pneumonectomy is utilized for neoplasms situated closer to the hilus. Furthermore, lobectomy is performed in patients who are considered poor risks. However, certain divergent trends are emerging, with some surgeons advocating conservation of pulmonary tissue and resection of the lymph nodes (Cahan; Overholt and Bougas) whereas others advocate an over-all aggressive approach (Watson; Weinberg).

Langston calls attention to the fact that since fourteen of his fifteen resected tumors presented evidence of blood vessel invasion, "further surgical refinements directed toward improving the survival of patients with bronchogenic carcinoma might well incorporate maneuvers designed to prevent vascular spread which could be related to the operation itself."

PALLIATIVE TREATMENT

The desire to do something definitive for a patient whose lung cancer is found to be inoperable at thoracotomy is great. Abbey Smith [1] advises palliative resection in all such instances. In his series of forty-eight consecutive palliative operations with an operative mortality of 20 per cent (his operative mortality for curative operations was 9 per cent) he was encouraged by the results—marked palliation following removal of the bulk of the affected tissue. Further assessment of palliative resection in the presence of a high operative mortality rate is necessary. The present authors have practiced interstitial irradiation

of those cancers found to be inoperable at thoracotomy (see Chap. 27).

COMBINED RADIATION THERAPY AND SURGICAL RESECTION

Bromley and Szur [15] of the Hammett Hospital (London), treated a series of patients by radical medium voltage radiation therapy, giving an average tumor dose of 4,700 r in 42 days. Sixty-six patients who had been considered inoperable became candidates for resection of their cancers; the operative mortality of this group was 10 per cent. Thirty-eight patients died with cancer present, and eleven are alive for variable periods, apparently free of cancer. This report calls attention to the fact that certain patients considered inoperable should be reevaluated as to their operability following radiation therapy.

PRESENT STATUS OF TREATMENT OF PULMONARY CANCER

Are more patients being cured of their pulmonary cancers today than in the past? Available data do not seem to indicate that they are, in significant numbers.

Churchill [23] states that though more patients come to operation (55 per cent of patients seen between 1950 and 1957 as compared with 43 per cent of those seen between 1930 and 1950) and the resectability rate has increased (35 per cent for the more recent series as contrasted with 25 per cent for the earlier series), there was no significant change in the survival rate of the two series, this remaining the same when the factor of operative mortality was excluded.

Burford, Ferguson, and Spjut [17] do not believe that patients with lung cancer are being seen earlier; in fact, the resectability rate at Barnes Hospital (St. Louis) has decreased. Between 1948 and 1952 the resectability rate was 39.5 per cent and in their later series, 1952-1955, the resectability rate was 32.3 per cent.

Bloomer and Lindskog [9] reported on three consecutive series of one hundred patients each, the first admitted to the New Haven Hospital between 1938 and 1943, the second between 1943 and 1946, and the third between 1947 and 1949. They concluded that

there is little reason for optimism concerning earlier diagnosis and the results of treatment. The average duration of symptoms before admission was the same for the three series (an over-all average of 7.4 months). There was a slight increase in the percentage of patients explored; there was a greater tendency to attempt palliative resection; 65 per cent of the patients explored in the third series had resections performed in contrast to 37 per cent in the first series. There was no great improvement in the five-year cure rate for the three series.

The over-all increase in the resectability

rate, the lowered mortality rate, and the observation that a significant number of patients have cancers limited to the lung should yield a higher five-year survival rate. The extremely low mortality rate associated with exploratory thoracotomy dictates that this definitive procedure be performed in any patient who is a cancer suspect. A current five-year survival rate of 34 per cent [59] for patients whose cancers are localized to the lung should stimulate every effort toward earlier and adequate treatment of patients harboring pulmonary cancer.

Radical Pneumonectomy in the Treatment of Bronchogenic Carcinoma

Including Dissection of Mediastinal Lymph Nodes

Joseph A. Weinberg

The ideal treatment of bronchogenic carcinoma consists of the total removal of the involved lung together with the thorough extirpation of its regional lymphatics and lymph nodes. Experience has shown that the planned removal of distant and obscured lymphatics is not only feasible but actually simplifies the procedure of pneumonectomy by clearly exposing the blood vessels of the hilus for their easier ligation and division [2, 4, 8, 16, 17]. A prerequisite for that part of the operation of radical pneumonectomy which concerns the removal of the regional lymph nodes is a knowledge of the mediastinal lymphatics; therefore, a large part of this chapter will deal with the location of the lymph nodes and their relationship to each other and to the lungs.

SURGICAL ANATOMY OF THE INTRATHORACIC LYMPH NODES

For the purposes of the surgeon, the mediastinal lymph nodes are best described by beginning with the nodes situated most peripherally within the thorax and progressing toward the nodes of the roots of the lungs, this being the order in which the lymphatics should be approached surgically in a well-planned operation for carcinoma (Figures 19-1 to 19-8).

Lymphatics of the Right Hemithorax

UPPER MEDIASTINAL LYMPH NODES

The upper mediastinal lymphatics include the nodes that are superior to the root of the lung.

Located at the highest region within the

thorax is the right anterior mediastinal group made up of the nodes at the termination of the subclavian vein, the nodes in front of the right innominate vein, and the nodes overlying the upper portion of the superior vena cava. There are also important lymph vessels along the course of the phrenic nerve in this region.

Medial and deep to the anterior mediastinal lymph nodes is a group of paratracheal nodes situated partly between the trachea and the superior vena cava, and partly between the trachea and the esophagus. The nodes in this group are in close relationship with the right recurrent nerve as it winds around the right subclavian artery.

The para-azygos nodes are situated at the junction of the azygos vein with the superior vena cava, one lying inferior and another lying superior to the azygos vein. The superior para-azygos node is not constant.

Medial and posterior to the para-azygos nodes are the lower paratracheal nodes, several in number, lying partly between the lower portion of the trachea and the superior vena cava, and partly between the pulmonary artery anteriorly, the trachea posteriorly, and the right side of the aortic arch medially.

In addition to these nodes, there are two principal chains of intercostal nodes, one situated posteriorly along the vertebral margin and designated as the paravertebral chain, and the other situated anteriorly along the sternal margin and described as the internal mammary chain. There are also inconstant nodes in the intercostal spaces midway between the two principal intercostal chains.

The lymph from the upper mediastinal

nodes terminates in the nodes of the subclavian triangle of the neck and in the lymph vessels that empty into the venous circulation at the confluence of the subclavian and internal jugular veins.

LOWER MEDIASTINAL LYMPH NODES

These comprise the nodes inferior to the root of the lung.

The lowermost nodes within the right hemithorax are the anterior diaphragmatic or paraphrenic, which lie just anterior to the inferior vena cava at the site of entrance of the phrenic nerve to the diaphragm. These nodes do not normally receive lymph from the lung, but they are included here because of the frequency of extension of bronchogenic cancer along this pathway. Also, a communication of this pathway with the lung can be demonstrated by means of vital staining.

Situated close to the undersurface of the inferior pulmonary vein are the nodes of the pulmonary ligament. This group of from one to three nodes lies embedded in areolar tissue between the pleural leaves which form the pulmonary ligament. For the purposes of the surgeon, these nodes may be regarded as forming a continuous chain with the paraesophageal nodes which lie along the right side of the esophagus. The paraesophageal chain in its entirety makes up the greater part of the posterior mediastinal chain.

The subcarinal (inferior tracheobronchial) group is a large aggregate of nodes that lies immediately under the carina and extends for a distance of approximately 2 cm. onto the undersurface of each bronchus. There are usually five to seven nodes in the group, as many as ten have been removed from this region during surgery. There is no line of demarcation between the right and left components, and they are best considered as a unit for surgical purposes. Most, if not all, of the subcarinal nodes are surgically accessible from either the right or the left hemithorax without entering the opposite pleural space.

LYMPH NODES OF THE PULMONARY HILUS

There are several prominent hilar nodes interspersed between the hilar vessels and the bronchus, and varying from five to ten in

number. Some are more easily approached from the anterior aspect of the hilus, and others from the posterior aspect. They are important surgically because most of the lymph from the lung passes through them before reaching the more distant mediastinal nodes.

Lymphatics of the Left Hemithorax

UPPER MEDIASTINAL LYMPH NODES

Located in the region of the cupola of the pleura and lying immediately under the parietal pleura are the nodes in the space between the subclavian artery and the common carotid artery, the nodes along the left side of the innominate vein, and the nodes on the anterosuperior aspect of the arch of the aorta. These nodes collectively comprise the anterior mediastinal group. The lymphatics accompanying the phrenic nerve in this region are important from the surgical view. Usually there are no lymph nodes along the upper thoracic portion of the phrenic nerve, but the lymph vessels that regularly accompany the nerve may act as pathways of spread of bronchogenic cancer.

Medial and deep to the anterior mediastinal nodes is the left paratracheal group situated along the left side of the trachea and partially obscured by the ascending and transverse portions of the aortic arch.

Approaching the hilus, the next collection of lymph nodes encountered is the important group within the space formed by the arch of the aorta and the left pulmonary artery. They are frequently the site of metastases in advanced cases of carcinoma of the left lung. These nodes will be described in succeeding paragraphs as the nodes of the aortic window. One of the nodes in this space lies between the ligamentum arteriosum and the recurrent nerve as the latter leaves the vagus nerve to pass around the aortic arch. The nodes of the aortic window merge with those lower paratracheal nodes that are partially obscured by the ascending portion of the aortic arch.

LOWER MEDIASTINAL LYMPH NODES

The diaphragmatic nodes, the lymphatics along the lower part of the phrenic nerve, and the nodes of the pulmonary ligament on the left side are arranged in a pattern almost

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The lymph from the upper mediastinal

exist between the anterior mediastinal nodes of the two sides; however, extension of carcinoma to the opposite side by way of this communication is relatively infrequent in the early stages of the neoplasm.

The lower paratracheal nodes, the right half of the subcarinal nodes, the inferior hilar nodes, the nodes of the pulmonary ligament, and the lower paraesophageal nodes all receive lymph from the lower half of the right lung, including the lower half of the middle lobe. The normal drainage is mostly through the inferior hilar nodes before reaching other groups, with some of the lymph passing to the paraesophageal nodes without the intermediation of the lower hilar nodes. The lymph then passes through the higher paratracheal plexus to reach the terminal lymphatics in the subclavian triangle.

Lymph from the parietal pleura is relayed chiefly through the diaphragmatic and intercostal lymphatics to the lymph nodes and lymph vessels of the subclavian triangle. These routes concern the surgeon in cases in which the cancerous lung becomes adherent to the parietal wall.

Communications with the lymphatics along the lower part of the phrenic nerve will be discussed under surgical pathology.

Pulmonary Lymphatics of the Left Hemithorax

The mediastinal nodes of the left hemithorax differ in several important respects from those of the right side. There are no veins on the left side that correspond to the superior vena cava and the azygos vein; hence, there are no corresponding paravenous nodes. Instead, there is the important group of nodes within the aortic window that receive lymph from the upper part of the left lung and relay it to the paratracheal and anterior mediastinal nodes.

Another noteworthy difference is that a part of the lymph from the lower half of the left lung is relayed through the subcarinal nodes to the right paratracheal nodes. This affords a second natural route for the extension of cancer from one side of the thorax to the other, the first being the communication between the anterior mediastinal nodes of the two sides, already described.

Except for the differences that have been noted, the general plan of drainage is the same for the left side as it is for the right.

A detailed knowledge of the direction of drainage of lymph from the several segments of each lung is important for an understanding of disease processes, but it is not particularly applicable in the performance of the operation of radical pneumonectomy. Cancer originating in any part of the lung may spread in any direction within the hemithorax, regardless of normal directions of drainage. To limit the lymphatic dissection according to the normal drainage pattern of the particular region of the lung that is involved would be as illogical as to limit the resection for breast cancer according to the quadrant of the breast that is involved. For this reason it is much more important for the surgeon to be familiar with the location of the several groups of regional lymph nodes of the lung than it is for him to know the details of the direction of the flow of lymph.

SURGICAL PATHOLOGY OF THE LUNG

In some respects carcinoma of the lung is more vulnerable to surgical attack than is carcinoma in other situations. Most of the regional lymphatics of the lungs are situated within their respective hemithoraxes, and although there are cross communications between the two sides, metastatic invasion by way of these cross routes is not commonly seen [9, 10]. It is not unusual to find that the gross evidence of bronchogenic carcinoma remains confined to the hemithorax even at the time of death of the untreated patient [14]. On the unfavorable side, the lymphatic spread may be in any direction within the hemithorax and, as often as not, it occurs along pathways contrary to the normal direction of lymph flow. An example of this is seen in the retrograde extension of carcinoma to the lymph nodes in juxtaposition with the phrenic nerve, often with resulting paralysis of the diaphragm.

Paratracheal and other mediastinal nodes may become so enlarged with metastases that they cause severe circulatory and respiratory embarrassment. Although metastases in this location would indicate that the carcinoma has extended beyond the bounds of curative

identical with that of the corresponding groups on the right side, and do not need further description. The left paracosophageal nodes lie between the descending aorta and the esophagus, and can be exposed only after ligating and dividing the overlying arteries that pass from the aorta to supply the esophagus. There are also small but significant arteries from the aorta that supply the paracosophageal nodes.

The hilar nodes correspond to those of the right side in their anatomic arrangement;

here is based on investigations made with vital staining of the lymphatics during surgery [16], on observations of the distribution of metastases to the lymphatics in advanced cases of bronchogenic cancer [6, 9, 10, 12], and on reviews of the works of Rouvière and of Delamere, Poirier, and Cunéo (Figure 19-1).

The lymphatics of the pulmonary parenchyma are divided into two plexuses: the superficial, which drains first to the pleura and then in the nodes of the hilus; and the

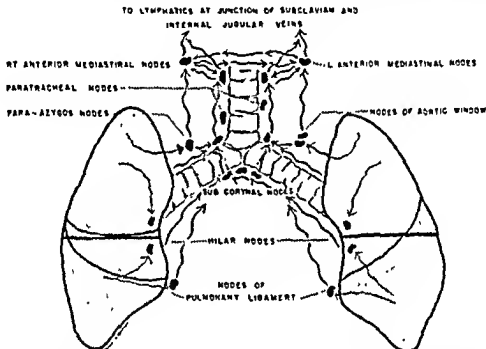


Fig. 19-1. Diagram of lymphatic communications between the lungs and the mediastinum

however, there are significant differences in pathways of drainage that will be discussed later.

The arrangement of the nodes of the parietal wall of the left hemithorax follows the same general pattern as that of the corresponding groups on the right side.

LYMPHATIC DRAINAGE OF THE LUNG

Only the gross description of the direction of the flow of lymph between the lungs and the intrathoracic lymph nodes will be given here, and the reader is referred to the works of Müller [11], of Rouvière [15], and of Delamere, Poirier, and Cunéo [5] for more detailed descriptions. The description given

deep, which drains through lymph channels and nodes along the blood vessels and bronchi within the lung to the hilus.

Pulmonary Lymphatics of the Right Hemithorax

The lymph from the upper half of the right lung passes to the para-azygos and paratracheal lymph nodes both directly and through the superior hilar nodes. Direct communications exist between the para-azygos nodes and the anterior mediastinal nodes, and between the paratracheal and the anterior mediastinal nodes. In the latter communication, lymph may pass in either direction between the two groups. Connecting pathways

and that the opportunity for surgical cure is greatly reduced, if it is not lost entirely.

TECHNIC OF RIGHT RADICAL PNEUMONECTOMY

The description given here is concerned particularly with the performance of the pneumonectomy and dissection of the mediastinal lymph nodes. Details concerning anesthesia, preoperative and postoperative care, bronchial closure, and ligation of major vessels are generally omitted. The reader is referred to Chap-

extending from the parasternal to the mid-scapular line, and the ribs are spread by means of a heavy-bladed self-retaining retractor of the Finocchetto type. It is not necessary to resect or divide any of the ribs if a long intercostal incision is used.

MEDIASTINAL AND HILAR DISSECTION

The mediastinum is carefully examined for evidence of gross lymphatic metastases, to determine whether or not a radical pneumonectomy should be attempted. Spread of

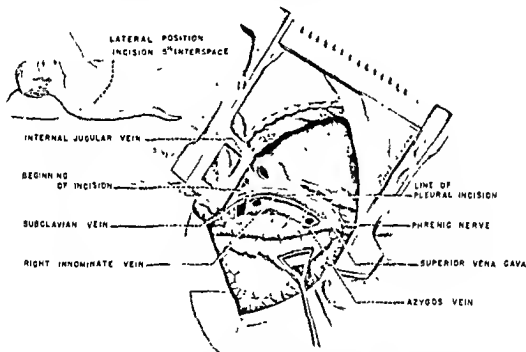


Fig 19-2 Right radical pneumonectomy, anterior mediastinal and para-azygos nodes. The dissection begins in the uppermost region in the right hemithorax. After obtaining exposure through the fifth intercostal space, the mediastinal pleura is incised from the cupola to the hilus of the lung to expose the mediastinal lymph nodes.

ters 13 and 14 for details of anesthesia and preoperative and postoperative care.

SURGICAL APPROACH

The true lateral approach is especially suited for exposure and resection of the mediastinal lymphatics and for division of the structures of the pulmonary root. However, no special difficulties are encountered with the anterior or posterolateral approach, and the choice may be left to the individual preference of the surgeon.

With the patient in the lateral position, an incision is made through the fifth interspace

cancer beyond the hilar nodes usually precludes any possibility of curative resection.

The resection begins with the mediastinal lymphatics in the uppermost portion of the hemithorax. An incision is made in the mediastinal pleura over the site of origin of the subclavian artery and it is extended along the superior vena cava to the hilus of the lung (Figure 19-2). This maneuver will expose the nodes in juxtaposition with the right subclavian artery and vein and the right innominate vein. These nodes and the nodes along the upper part of the phrenic nerve, which together constitute the anterior mediastinal

extirpation, it is justifiable in some instances to remove the enlarged nodes in order to relieve the pressure that they exert on the trachea and the great vessels.

Cancerous invasion of the costal wall occurs most often as a result of fusion of a peripheral cancer of the lung to the parietal pleura. The invasion of the ribs and soft tissues takes place by direct extension and by lymphatic infiltration, with the latter probably occurring through newly formed lymphatic anastomoses in the adhesions between the lung and the parietal wall [13]. In this situation, it is possible to stain intercostal nodes by injecting a vital dye into the lung near the site of its abnormal attachment to the thoracic wall. It is not possible to stain the intercostal nodes by this method in the absence of adhesions between the lung and the costal wall. Adhesions that may contain cancer are of particular concern to the surgeon who is intent on performing an adequate operation. It must be assumed in these cases that the cancer has invaded the thoracic wall beyond the pleural membrane and that an adequate operation must include a generous portion of the thoracic wall to the subcutaneous tissue, together with the anterior and posterior chains of intercostal lymph nodes (see Chap. 23).

Involvement of the ribs and vertebrae may be logically explained on the basis of extension of the carcinoma by way of the lymphatics. If the bony involvement occurred as the result of hematogenous spread, one would expect unpredictable and distant involvement to be commonplace. Instead, the most frequent sites of osseous involvement are the ribs and the vertebrae [10]. Burke [3] has shown that lymph channels in the parietal pleura communicate with the lymph channels of the thoracic wall, and that lamp black and fluorescent colloids injected into the pleural space are taken up in sufficient quantity to be demonstrable five days later in the parasternal and paravertebral nodes. He also found in reviewing a group of cases of tuberculous cases of the spine that pleuritis is frequently a precursor of the disease, and that there is good reason to believe that the vertebral involvement has its origin in involvement of the nodes that are in juxtaposition with the bodies of the involved vertebrae. This line of rea-

soning applies equally well to the spread of bronchogenic cancer. Costal involvement is not a contraindication to surgery if the mediastinal nodes are not grossly involved and the thoracic wall can be excised en bloc well beyond the gross evidence of the cancer. In this situation, the surgeon assumes that there is a potential or actual involvement of the anterior and posterior chains of intercostal nodes and deals with them accordingly. These chains are rarely involved with metastases of bronchogenic carcinoma in the absence of adherence of the primary cancer to the thoracic wall.

Involvement of the cervical sympathetic plexus, resulting in a Horner's syndrome, and involvement of the recurrent nerve are almost always contraindications to surgery because of the likelihood that the carcinoma has extended beyond the field of surgical exposure.

Comment should be made here on the role of lobectomy. It is evident from the unpredictable extensions of bronchogenic carcinoma that lobectomy cannot be regarded as more than a palliative procedure. An adequate removal of the lymphatics cannot be performed with a partial removal of the lung, since many of the nodes would remain obscured and inaccessible as long as one of the lobes remains. Even if it were possible to remove the nodes that are known to be in the pathway of the normal flow of lymph from the involved lobe, the procedure would fail in its purpose because the direction of spread of carcinoma is frequently retrograde and otherwise contrary to the normal direction of flow. There are instances in which the resection must be limited to lobectomy because of the poor respiratory function of the patient. In these cases the resection is to be regarded as a limited procedure for the handicapped patient who cannot tolerate the removal of an entire lung.

The ideal method of dealing with the lymphatics in the surgical treatment of cancer of the lung is to anticipate which nodes are most likely to become involved, and deal with them before they show gross evidence of metastases. Once the involvement of the nodes is apparent to the naked eye it is almost certain that microscopic extension has occurred to distant nodes beyond the reach of the surgeon,

with the nerve and its associated lymphatics to assure the wide removal of the latter structures.

The pleura over the anterior aspect of the hilus is now incised close to the pericardium, and the pulmonary artery is freed in its circumference. It has already been exposed in the greater part of its course during the removal of the lower paratracheal nodes and all that remains is to separate it from the superior pulmonary vein. This is accomplished by finger and forceps dissection. The pulmonary

The surgeon now leaves the upper field and directs his attention to the region of the branching of the phrenic nerve on the surface of the diaphragm, just anterior to the inferior vena cava. The nodes in this location and the areolar tissue in which they lie are dissected from the diaphragm and are carried in continuity with the phrenic nerve and its associated lymphatics to the pulmonary root in the same manner as described for the dissection of the upper part of the nerve (Figure 19-5). In the course of this separation the one or two

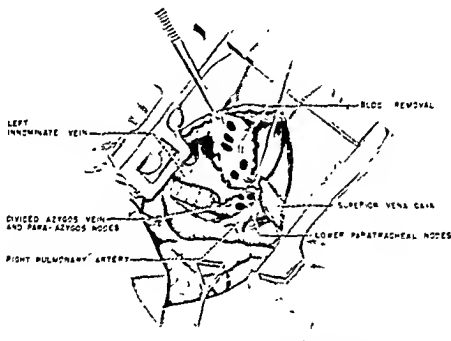


Fig 19-4. Right radical pneumonectomy. Para-azygos and lower paratracheal node dissection. The azygos vein has been divided between ligatures and the para-azygos nodes (barred figures) have been excised. The lower paratracheal nodes are exposed for removal by retracting the lower part of the superior vena cava medially. Following the lower paratracheal dissection, the pulmonary artery is divided between transfixion sutures and ligatures.

artery is now ligated and transfixed proximally and distally, and divided. The division is made close to the mediastinum to assure a thorough removal of the lymph nodes from this region. The nodes that remain attached over the pulmonary artery are dissected toward the lung to maintain the block resection. At this stage the bronchus, which lies clearly exposed in the field of operation, is occluded by means of a heavy ligature to prevent secretions from entering the opposite bronchus.

nodes situated near the phrenic nerve as it lies on the pericardium are included. It is not necessary to remove the full thickness of the pericardium to accomplish the removal of the lymphatics that accompany the phrenic nerve in this region. On reaching the hilus the nerve is dissected toward the lung in order to maintain the dissection in continuity.

The pulmonary ligament is now divided close to its attachment to the pericardium. The right side of the esophagus is exposed at the same time so that all of the nodes within

group, are excised together with areolar tissue in which they are embedded (Figure 19-3). This is accomplished, as much as possible, by sharp dissection. Blood vessels to the larger nodes are divided between clamps and ligated. The upper part of the superior vena cava is now retracted medially to expose the higher right paratracheal nodes (Figure 19-3). These

Oozing from very small blood vessels that continues for more than two or three minutes is controlled by the application of processed fibrin moistened with thromboplastin.

The azygos vein is now cleared of its overlying pleura and is divided between ligatures. The one or two nodes lying at the junction of the azygos vein with the superior vena cava

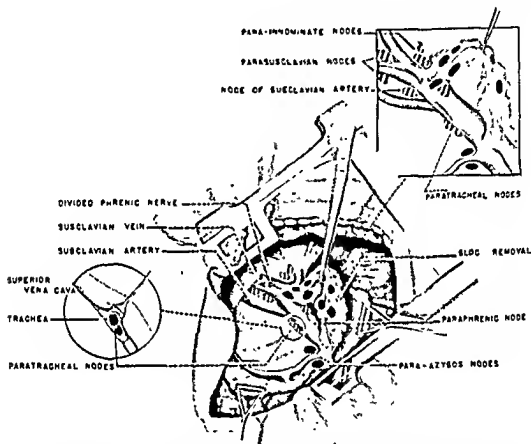


Fig 19-3 Right radical pneumonectomy. Anterior mediastinal and upper paratracheal node dissection. The parasubclavian, parainnominate, upper paratracheal, and paraphrenic lymph nodes have been resected en bloc. The superior vena cava has been retracted medialward (lower inset) to expose the upper paratracheal nodes. In this illustration and in those that follow, the barred figures indicate sites from which nodes have been removed. The nodes included in en bloc dissection and those not yet excised are indicated by solid-black figures.

nodes, which lie in the space between the trachea and the vagus nerve, are removed in continuity with the subclavian and innominate nodes, thus maintaining the block dissection. An attempt is made to include a node that lies deeply posterior and medial to the beginning of the subclavian artery. This node, which is the highest of the paratracheal group, lies in close relationship with the vagus and recurrent nerves. The nerves are identified and protected during this phase of the dissection.

are excised either before or after dividing the azygos vein. The lower half of the superior vena cava is retracted medially to expose the lower paratracheal nodes which lie between the superior vena cava and the trachea, and between the right pulmonary artery, the right side of the aortic arch, and the trachea (Figure 19-4). The phrenic nerve and its accompanying blood vessels, lymph channels, and lymph nodes are dissected free to the hilus. A strip of mediastinal pleura is included

this region may be brought into view and included in the resection (Figure 19-5). Although a distinction is made between the nodes of the pulmonary ligament and the paraesophageal nodes in most anatomic descriptions, they are best considered as a single aggregate for surgical purposes.

The hilar nodes in juxtaposition with the pulmonary veins are exposed and dissected toward the lung (Figure 19-6). After bring-

lished. It cannot be overemphasized that the ligation of the major vessels of the pulmonary root should always be performed proximal to their branchings in order to include all the hilar nodes.

There remains the important group of subcarinal nodes that lie under the carina and the right and left bronchi. They are exposed by retracting the lung laterally (Figure 19-7). The resection of these nodes is started on the

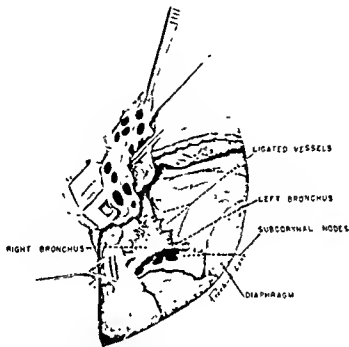


Fig 197 Right radical pneumonectomy Dissection of the subcarinal nodes The subcarinal nodes are the final group to be removed before dividing the bronchus, which is the only remaining bridge between the lung and mediastinum This group of nodes is exposed by retracting the lung laterally The dissection includes the nodes on the undersurface of the bifurcation of the trachea and on the undersurface of the right and left main bronchi

ing the inferior pulmonary vein clearly into view, it is divided between ligatures and transfixion sutures. The division is made between the pericardium and the first branching of the vein. If the extrapericardial portion of the vein is short, it is divided within the pericardial sac to permit the thorough removal of the lymphatics in this region [1, 7]. The superior pulmonary vein is dealt with in the same manner. Hilar nodes that lie on the posterior aspect of the root of the lung are dissected away from the mediastinum toward the lung, if this has not already been accom-

plished. The subcarinal nodes are the final group to be removed before dividing the bronchus, which is the only remaining bridge between the lung and mediastinum. This group of nodes is exposed by retracting the lung laterally. The dissection includes the nodes on the undersurface of the bifurcation of the trachea and on the undersurface of the right and left main bronchi. The subcarinal nodes are the final group to be removed before dividing the bronchus, which is the only remaining bridge between the lung and mediastinum. This group of nodes is exposed by retracting the lung laterally. The dissection includes the nodes on the undersurface of the bifurcation of the trachea and on the undersurface of the right and left main bronchi.

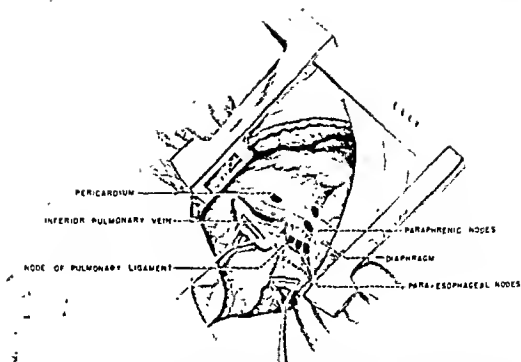


Fig. 19-5. Right radical pneumonectomy The lower mediastinal dissection begins with the freeing of the phrenic nerve and its associated lymph nodes from the diaphragm and pericardium. The nodes of the pulmonary ligament and the paraesophageal nodes are exposed for removal by dividing the pulmonary ligament close to the pericardium.

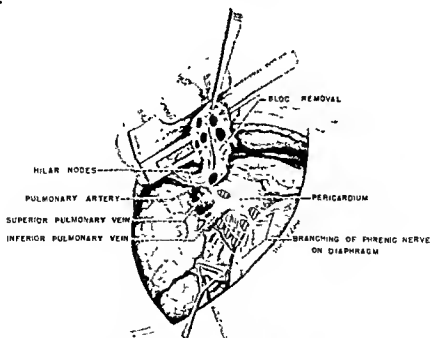


Fig. 19-6 Right radical pneumonectomy Dissection of the hilar nodes. The paraphrenic and paraesophageal nodes, and the nodes of the pulmonary ligament (barred figures), have been resected en bloc. The hilar nodes are exposed anteriorly and posteriorly and are resected concomitantly with the ligation and division of the pulmonary veins. (Only the anterior hilar exposure is illustrated.)

dissection. A part of the lymph from the lower half of the left lung drains to the right paratracheal nodes by way of the subcarinal nodes; therefore, from a theoretic consideration, it is more important that the right half of the subcarinal nodes be removed in performing a radical left pneumonectomy than that the left half of the subcarinal nodes be removed in performing a radical right pneumonectomy. Actually, experience indicates that thoroughness in the subcarinal dissection

cancer has extended through the parietal pleura by direct invasion or through newly formed lymphatic channels [13]. If the surgeon does not find evidence of extensive involvement of intercostal nodes, and the cancer is in a location that permits wide removal of the costal wall beyond the limits of the lesion, the first stages of the operation are proceeded with in the manner that has been described for the mediastinal dissection and the amputation of the lung. During these

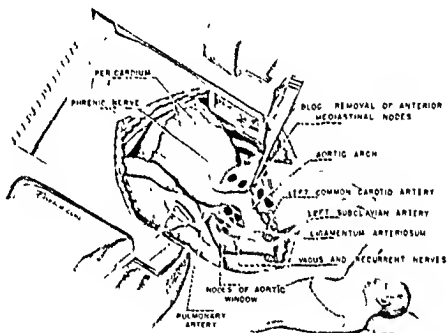


Fig 19-8. Left radical pneumonectomy Upper mediastinal region. After excising the anterior mediastinal, paraphrenic, and upper paratracheal lymph nodes (barred figures), the nodes of the aortic window are removed. This dissection is facilitated by dividing the ligamentum arteriosum between ligatures. Injury to the recurrent nerve is guarded against during this phase of the dissection. The lower mediastinal lymph node dissection is essentially the same as for the right hemithorax.

is equally important in dealing with cancers of the right lung, since cases that come to necropsy occasionally show evidence of spread from the right lung to the left paratracheal nodes through the intermediation of the subcarinal nodes.

RADICAL PNEUMONECTOMY WITH INCLUSION OF A PORTION OF THE COSTAL WALL

Invasion of the costal wall by cancer is not necessarily a contraindication to radical surgery. In these cases it is assumed that the

stages of the operation the lung is left attached to the thoracic wall in order to maintain the block dissection (Figure 19-9).

After completion of the nodal dissection and the amputation of the lung, incisions are made through the parietal pleura in a quadrangular design well beyond the limits of the attachment of the lung to the parietal wall. The latitudinal incisions are made at least one full costal segment beyond the site of the carcinomatous attachment. The longitudinal incisions are made beyond the anterior and posterior intercostal lymphatic chains so that

ralization of the bronchial stump cannot be accomplished. There has been no increase in the incidence of bronchial fistula since we have abandoned the procedure of pleuralizing the bronchial stump. On the contrary, the incidence has decreased, owing probably to improvements in the technic of suturing the bronchial stump.

POSTOPERATIVE DRAINAGE

The operation of radical pneumonectomy reopens the question of whether or not postoperative drainage of the pleural space should be used. Extensive removal of the mediastinal pleura frequently results in emphysema of the thoracic wall, neck, and arms owing to expansion of the air that is trapped in the pleural space. Although the emphysema is limited in its extent and severity, the discomfort and apprehension it causes in the patient make it advisable to provide drainage during the first two or three days following operation. This is done by introducing a right-angled No. 32-French rubber catheter into the third interspace anteriorly at the mid-clavicular line and connecting it with a water-seal bottle placed at floor level. By this simple expedient, air remaining in the pleural space after closure of the thoracic wall will escape through the tube rather than into the parietal tissues through the depleuralized mediastinum. An alternative to the use of closed intercostal drainage is occasional needle aspiration of the pleural space during the first two or three postoperative days.

TECHNIC OF LEFT PNEUMONECTOMY

An intercostal incision is made in the fifth space in the same manner as described for the right side. After freeing the lung from existing adhesions that are considered to be free from cancerous invasion, the operation within the thorax is begun at the pleural cupula.

MEDIASTINAL AND HILAR DISSECTION

An incision is made through the parietal pleura at the apex and is carried downward to the hilus of the lung, following a course parallel and 1 cm lateral to the phrenic nerve, at first over the left innominate vein and then over the right side of the arch of the aorta.

The nerve and its associated blood vessels and lymphatics are divided at their highest point within the thorax and are dissected toward the hilus with the strip of mediastinal pleura to which they are fixed. The left innominate vein and the origins of the common carotid and subclavian arteries are exposed, and the anterior mediastinal nodes and areolar tissue in the region are excised. The nodes included in this part of the resection are a subclavian node between the subclavian and common carotid arteries at their origins, nodes along the left side of the left innominate vein, and a node on the supreme aspect of the aortic arch. Blood vessels that supply the lymph nodes are ligated and clamped as they are encountered.

Continuing the dissection inferiorly, the left paratracheal nodes that lie along the lateral and posterior aspects of the trachea are removed as thoroughly as the overlying arch of the aorta will permit. The dissection now centers on the important region of the aortic arch (Figure 19-8). The nodes in the aortic window (the space bounded by the aortic arch above and the pulmonary artery below) are thoroughly removed together with their adventitia. During this part of the dissection great care is exercised to avoid injury to the recurrent nerve as it winds around the aorta. It is advisable to divide the ligamentum arteriosum between ligatures to facilitate the exposure and removal of the nodes in juxtaposition with it. By continuing the dissection deeply into the space, it is possible to remove most if not all of the left paratracheal nodes that have not been removed in the higher dissection. It is usually not possible to recognize a dividing line between the right and left lower paratracheal nodes while performing this part of the dissection, and caution should be exercised against carrying the dissection so far to the right that there is danger of entering the right pleural space. The difficulty of removing the nodes in this region is the weakest link in the left mediastinal dissection.

The remainder of the dissection is performed in the same manner as for the lower and middle portions of the mediastinum and hilus on the right side. One special point should be stressed in regard to the subcarinal

be rewarding. Of twenty-five radical pneumonectomies performed in our clinic from 1948 to 1953 for resectable bronchogenic carcinoma, the trend in terms of longevity has been very favorable. Eleven of the patients were alive five years or more after operation. Seven of these remain alive with no evidence of cancer for periods of five to eight years. Only two of the patients surviving more than five years showed evidence of cancer at the time of death. Both of these patients had evi-

dence of spread of cancer beyond the lung at the time of pneumonectomy. Two other patients who showed metastases at the time of resection remain alive and well, one for five years, the other for seven years. While these numbers are small, they show a greater percentage of survivals than corresponding groups of cases in which simple pneumonectomy was performed. These results were accomplished with a surgical mortality of 12 per cent.

those nodes will be included in the resection. The ribs that are to be sacrificed are divided anteriorly at or through the costal cartilages and posteriorly at their attachments in the transverse processes of the vertebrae. The cor-



Fig. 19-9. Radical resection of the lung with a portion of the thoracic wall. In this case, the cancer of the lung was adherent to the fourth rib. The third, fourth, and fifth ribs, with the parietal pleura, anterior and posterior intercostal nodes, and the muscles overlying the resected ribs, have been removed with the lung and the regional lymphatics en bloc. (From J. A. Weinberg [16], courtesy *Journal of Thoracic Surgery*.)

responding intercostal vessels and nerves are divided between clamps and are ligated, and the block dissection of the parietal wall is continued through the muscles and fascia overlying the ribs, leaving only the skin and subcutaneous tissue to cover the defect in the thoracic wall (Figure 19-10). If the tumor is situated close to the vertebral column, it will not be possible to remove the lymphatics as effectively as one would wish to, and it may be necessary to limit the operation to a less extensive excision of the wall. If this expedient is resorted to, the site of the invasion of the thoracic wall is marked with indelible ink on the skin surface, so that x-ray therapy may be directed to the region within the weeks following surgery.

GENERAL REMARKS REGARDING RADICAL PNEUMONECTOMY

Planned resection of mediastinal lymph nodes as a part of the operation of pneumonectomy for bronchogenic carcinoma is so recent a development that there has not been a sufficient number of operations, nor has there been a sufficient lapse of years, to warrant an evaluation of the results in terms of longevity. All that can be said at this time on the basis of results is that radical mediastinal resection can be accomplished without unreasonable surgical hazard to the patient. Many years of experience with a large number of operations will be required to determine whether or not the inclusion of regional lymphatics in the operation of pneumonectomy for cancer will

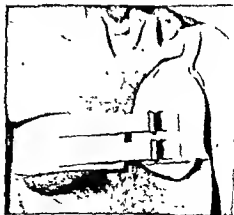


Fig. 19-10. (Left) Castal defect resulting from radical resection including part of the thoracic wall. (Right) Stabilization of the thorax by means of a tailored soft leather pad applied over the defect.

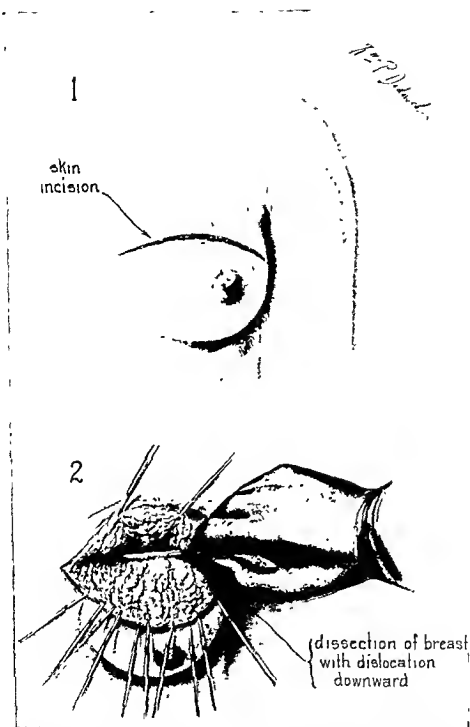


Fig 20-1. Location of skin incision. The incision is in the region normally covered by the brassière in the female. It is of course possible to make this incision below the nipple line and dislocate the breast upward instead of downward. (From W. F. Rienhoff and E. N. Broyles, courtesy *Journal of the American Medical Association*.)

Anterior Approach for Resecting Cancer of the Lung

William F. Rienhoff, Jr.

The successful treatment of malignant tumors of the lung and of those benign tumors which involve the primary bronchus rather extensively, can be accomplished only by complete removal of the lung together with its lymphatic vessels and lymph nodes. In the treatment of malignant tumors, lobectomy has been uniformly unsatisfactory owing to local recurrences. Any plan of operation should take into consideration the fact that in the majority of cases it will be necessary to amputate the primary bronchus close to the trachea in order to circumvent the tumor. This can be accomplished only by total pneumonectomy.

OPERATIVE TECHNIC

EXPOSURE OF HILUS OF THE LUNG

Access to the hilus of the lung by the anterior route has been found to have many advantages. The incision is made over the third intercostal space, anteriorly, extending from the lateral border of the sternum to the anterior axillary line (Figure 20-1). After dividing the pectoral muscles, the internal intercostal muscles are incised about midway between the third and fourth ribs, thus avoiding the intercostal vessels and nerves (Figure 20-2). The pleural cavity is quickly opened by cutting through the parietal pleura for the entire length of the incision and the opening into the chest is further widened by means of a self-retained retractor or rib-spreader (Figure 20-3). Thus, complete exposure of the hilus of the lung is obtained with minimum operative trauma and loss of time. Resection of the ribs is entirely unnecessary because

anteriorly the ribs are farther apart than elsewhere in the thoracic cage; and furthermore, if the proper type of rib-spreader is used, they may be disarticulated at the costochondral junctions by gently spreading the retractor blades farther apart. Disarticulation of the costochondral junction of the third and fourth ribs is accomplished with ease and rapidity. If further exposure is desirable, the incision may be lengthened laterally to the midaxillary line and with a retractor possessing a deeper blade the second and fifth ribs, as well as the third and fourth, may be readily disarticulated. When the ribs are reapproximated during closure, they are realigned with the costal cartilages and held in position by means of pericostal sutures (Figure 20-14).

The anterior approach permits rapid inspection to note whether invasion, or lack of invasion, of the hilus of the lung and mediastinum has occurred, even when the remainder of the pleural cavity is practically sealed off by adhesions. The rapidity of the opening of the thoracic cavity is greater. A truly high ligation of the pulmonary artery in the mediastinum, performed with great facility and celerity through the anterior incision, can be accomplished only with difficulty by a posterior approach because the pulmonary artery arises anterior to the primary bronchus (Figure 20-4). On this point hangs the ability to ligate the bronchus high up near the bifurcation of the trachea, insuring the safety and efficacy of a pneumonectomy, especially when the tumor approximates the carina. (See Chap. 21 for a discussion of the prone position in thoracic surgery.)

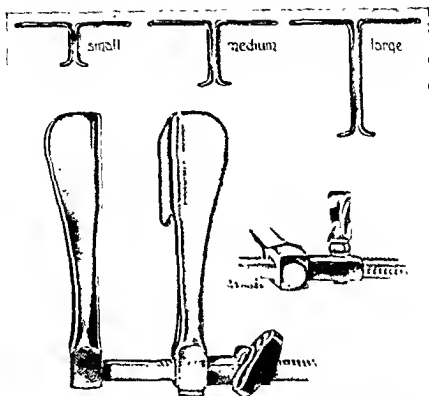


Fig. 20-3. Self retaining retractors with different sized blades and the set screw to hold the retractor at any particular point of spread of the blades. (Reduced to one half actual size)

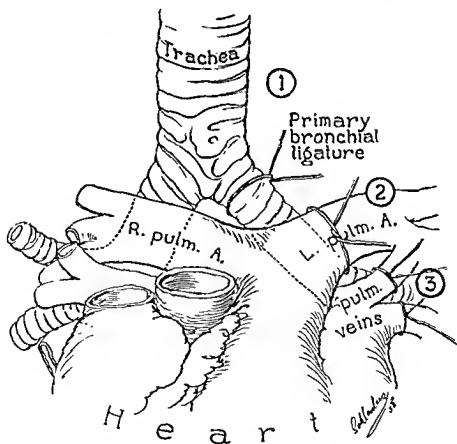


Fig. 20-4. Relation of primary bronchi to pulmonary arteries and veins. Various points at which ligatures are placed are designated by numbers 1, 2, and 3. 1 shows the site of the primary encircling ligature of the main bronchus, or step 2 in the operation. The first step is placing the ligature about the pulmonary artery at point 2 in the diagram. The third step in the operation consists in ligating the pulmonary veins, point 3.

LIGATION OF THE PULMONARY ARTERY

In the beginning of the operation, the mediastinal pleura is incised and dissected medialward together with the underlying areolar tissue, thus exposing the pulmonary artery (Figure 20-5). The point at which the mediastinal pleura is incised varies, depending

the superior and posterior surfaces are freed from the underlying bronchus (Figure 20-8). The inferior surface is then dissected away from the upper border of the superior pulmonary vein and a No. 10 oiled braided-silk ligature is passed around the mediastinal portion of the vessel at least 2 to 3 cm.

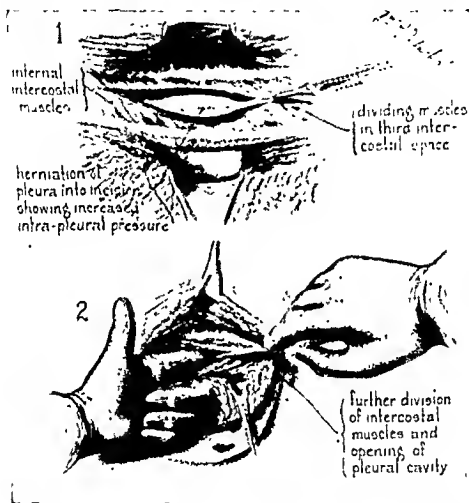


Fig 20-2. Division of the pectoral muscles with the internal intercostal muscles incised about midway between the third and fourth ribs, thereby avoiding the intercostal vessels and nerves.

upon whether the operation is performed on the right or the left side. On the right side, the guiding landmark is the azygos vein, since the right pulmonary artery emerges into the pleural cavity just inferior to this structure (Figures 20-5 and 20-6). On the left side, the pulmonary artery runs beneath the arch of the aorta (Figures 20-6 and 20-7). The upper or superior surface of the pulmonary artery is immediately exposed and by means of careful blunt dissection, mainly with the index finger,

proximal to its intrathoracic branches (Figure 20-9).

After the first ligature is tied, another is placed about the vessel 0.5 cm. distal to the primary ligature and this is likewise tied in a square knot. The loose ends of these ligatures are cut at least 6 cm. long so that they and the obliterated pulmonary artery may be easily recognized if a second-stage operation is found to be necessary. The phrenic nerve is crushed in order to allow a temporary eleva-

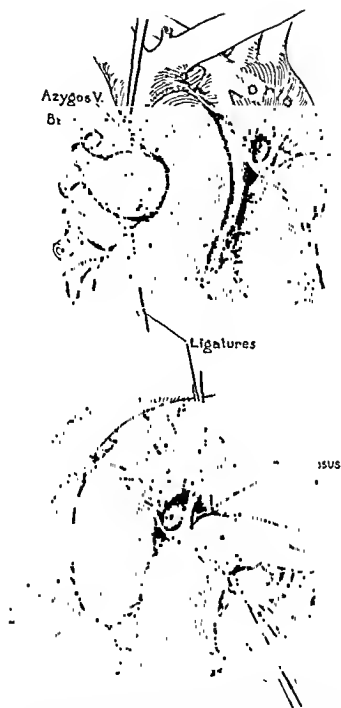


Fig 20 6. Diagrammatic sketch showing location of the ligatures for the right and left pulmonary arteries. These are placed around each artery in the mediastinum, proximal to the intrathoracic bronches.

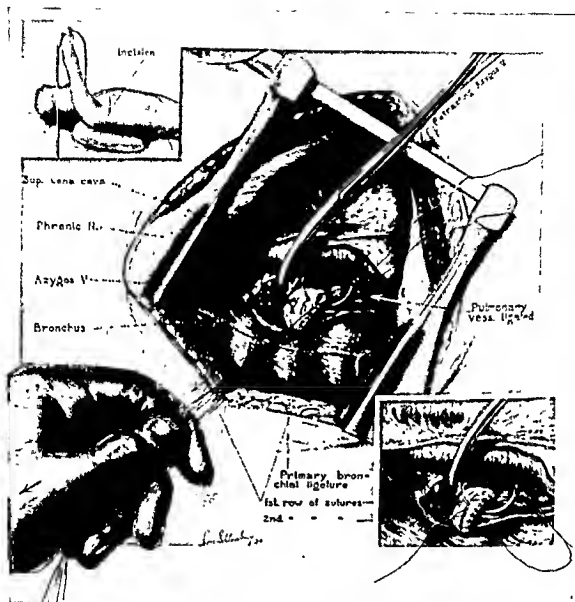


Fig 20-5. The upper left inset shows the position of the patient on the operating table. The side to be

pleted row of interrupted silk sutures closing the end of the bronchial stump is shown. Immediately above the curve of the needle may be seen the ligated end of the right pulmonary artery and below it the ligated ends of the superior and inferior pulmonary veins. In the lower right inset the second incomplete row of mattress sutures is shown. When the posterior membranous portion of the bronchus is sutured to the anterior cartilaginous wall, there is a tendency toward flattening of the stump. This brings about a more nearly perfect approximation of the mucous membrane of the bronchus, with a minimum amount of tension on the suture line. The primary encircling ligature may be seen again, as in the middle drawing, higher up on the main bronchus.

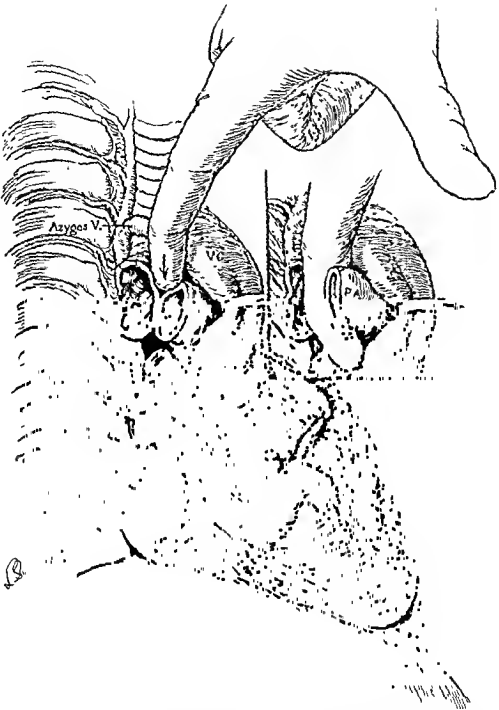


Fig 208 Diagrammatic sketch demonstrating the method of dissecting the pulmonary artery from the anterior surface of the primary bronchus. The anatomic relations of the primary bronchus and pulmonary artery are shown.

tion of the diaphragm with consequent partial obliteration of the thoracic cavity on the affected side.

LIGATION OF THE PRIMARY BRONCHUS

The primary bronchus is then stripped of all the bronchial lymph nodes and peri-

on their surface. The divided bronchus is closed with interrupted silk sutures.

LIGATION OF THE PULMONARY VEINS

The pulmonary veins are then doubly ligated with medium "c" silk. If, however, the decision has been made to grade the opera-

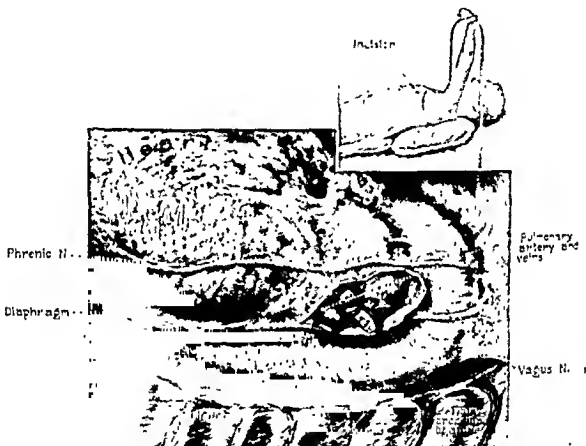


Fig. 20-7. The right upper inset shows the position of the patient for left total pneumonectomy. In the center drawing the amputated hilus of the lung is demonstrated. The ligated pulmonary artery and veins are visible above the bronchial stump. The primary encircling ligature of the bronchus may be seen proximal to the secondary suture line closing the amputated stump. In this patient the redundant mediastinal pleuro was employed to close over the hilar structures. The proximity of the vagus and phrenic nerves is shown. The ease with which they may be exposed is evident.

bronchial connective tissue from the bifurcation of the trachea to the point at which the pulmonary artery crosses the bronchus and takes up a position posterior to this structure. The bronchial nodes are more easily detected than lymph nodes elsewhere in the body, and because of their black pigmentation, metastases to them, as a rule, appear as white spots

tion into two or more stages, then the ligatures may be placed loosely about the veins and left untied, for the bronchial veins alone are of insufficient size to carry off from the lung the blood supplied by even the bronchial artery, or arteries. If the flow of blood through the pulmonary veins, either the superior or inferior, is in any way interfered with, moist

of dissection of the mediastinal lymph nodes.)

The bronchus is cut across in the mediastinum, not far from the bifurcation of the trachea and the primary encircling ligature (Figures 20-5 and 20-7). The incision is made slightly obliquely to the long axis of the bronchus, on a line running from above and lateral, to below and medial. The cut edge of the stump forms an angle of about 45 degrees with the superior border of the primary bronchus, and of about 135 degrees with its

branous wall is not only snugly fitted to the inner surface of the semicircular ring at all points, but also, as a result of the way in which the sutures have been placed, the membranous portion is rolled over the cartilaginous cut edge in a manner corresponding to the inversion of the intestinal wall. The cut ends of the mucous membrane are thus approximated on the inside of the blind-end stump. This method of closure of the cut ends tends to flatten out the horseshoe-shaped



Fig. 20-10. Use of pleural pedicle flap to cover the stump of the amputated bronchus. In this drawing the stump of the right primary bronchus is being covered. The primary and secondary encircling ligatures higher up on the bronchus are shown.

inferior medial border. In addition to the slanting direction of the incision across the bronchus, the cut is made on the bias so that the posterior membranous portion is a trifle longer than the more anterior cartilaginous wall. Interrupted fine "a" silk sutures are then placed in the membranous portion in such a way that the curved needle picks up a portion of the posterior membranous tissue a few millimeters proximal to the cut edge. The needle is then inserted into the cut edge of the mucous membrane and the cartilaginous ring of the bronchus directly opposite (Figures 20-5 and 20-7). From ten to twelve of these sutures are laid in a fan-shaped pattern. Therefore, when the knots are tied, the relaxed and relatively tough posterior mem-

bronchial cartilage rather than constrict it and, therefore, no tension whatever is placed upon the suture line. Two parallel rows of through-and-through sutures are placed proximal to the above-mentioned interrupted row. They are separated from the end and from each other by the width of the cartilaginous ring. The suture passes completely through the bronchial wall between the cartilaginous rings. These proximal sutures consist of No. 1 chromic catgut, because this would be less likely to cut through the posterior membranous layer than silk. Additional rows of these interrupted mattress sutures may be employed whenever necessary. One row contains about eight sutures (Figures 20-5 and 20-7).

The posterior membranous portion of the

gangrene of the respective drainage bed will ensue, unless the lung is removed without delay. The ligation of the pulmonary veins may be considered the third step in the operation.

tion of the veins the operation must be completed. If the patient is in good condition, exposure for amputation of the bronchus is better when the veins are divided.

Amputation of the hilus of the lung is per-

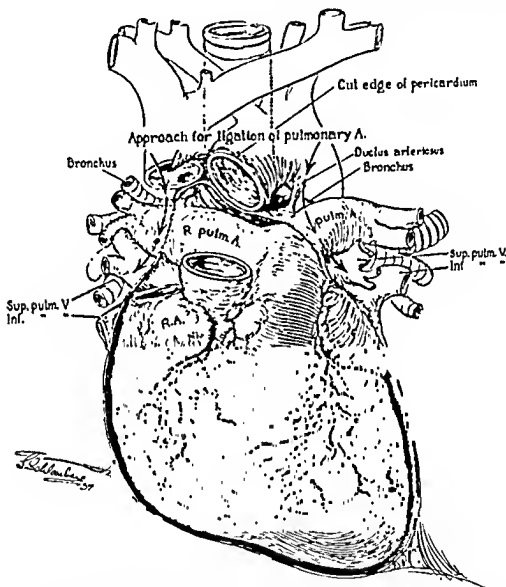


Fig 20-9. Diagrammatic sketch demonstrating the relation of the pulmonary artery to the reflections of the pericardial sac. The conus arteriosus and pulmonary aorta are within the pericardial sac, whereas the right and left pulmonary arteries run their entire course outside of and posterior to the pericardial sac. The right pulmonary artery is lower than the left.

AMPUTATION OF THE PRIMARY BRONCHUS

Amputation of the main bronchus constitutes the fourth step in the operation. This step may be taken prior to the ligation of the pulmonary veins (step 3) if there is doubt about being able to complete the operation in one stage, for, as mentioned above, after ligation

from above downward on the left, and from below upward on the right side. Only that portion of the vessels—pulmonary veins and artery—lying distal to the ligatures need be clamped. No lung or peribronchial tissue or lymph nodes should be left behind. If such is the case, a complete pneumonectomy has not been performed. (See Chap. 19 for details

human bronchus is ample to line, as it were, the entire semicircle of the anterior cartilaginous ring. Occasionally on the left side it may be helpful to leave a bit more of the underlip of the membranous portion to curl back over the cut end. The membranous wall of the bronchus is abundantly supplied with blood by the bronchial artery.

(See Chap. 15 for technique of resecting the trachea.)

After the suturing has been completed, it is well to cover the stump of the bronchus

of the relaxed, paralyzed diaphragm which at the second-stage operation will be found to lie almost against the bronchial stump. The tissue is sutured to the free end of the bronchus, thus retaining its viability from the base through which it is normally attached to the diaphragm. On the left side, still other tissue is available in some cases; for example, the upper portion of the pericardial sac serves adequately, but here, too, the diaphragm may be used. The procedure of supplementing the healing process of the bronchial stump by

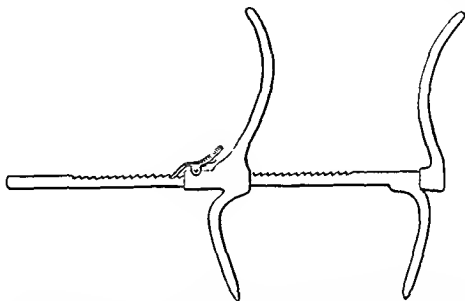


Fig. 20-13. Instrument used for the reapproximation of the ribs to hold them in place while the pericostal sutures are tied. The spike-like bills are inserted above and below the ribs to be approximated. They are then drawn together and held in position by means of the ratchet.

with some available additional tissue (Figure 20-10). A pedicle flap taken from the mediastinal pleura, with some underlying areolar tissue, has been found available in many patients on either the right or the left side. This flap may be slightly twisted or reflected upon itself, leaving the base attached in order to preserve its circulation. The free end may then be sutured to the bronchial stump. The division of the bronchus having been made high in the mediastinum, the stump is surrounded, while healing, with the more vigorous growth of the mediastinal areolar granulation tissue (Figure 20-11). As an alternative, on the right side a small but sufficiently large pedicle flap, about 6 by 2.5 cm., has been cut away from the superior portion

suturing it to some adjacent supporting tissue is a most valuable adjunct to insure primary and complete healing of the bronchus (Figure 20-12).

CLOSURE

Closure of the wound is accomplished by drawing the ribs together by means of a rib approximator (Figure 20-13) which holds them in position while perichondral sutures, usually three in number, of No. 10 braided silk are placed and tied. No attempt is made to suture the pleura or intercostal muscles. The regeneration of the former and the healing of the latter require only a few weeks. The pectoral fascia is drawn together with interrupted medium silk while the skin is closed



Fig. 20-11. Another method of using pleura to cover the proximal stump. In some patients the mediastinal pleura is so redundant that it is not necessary to cut the pedicle flap; in these cases the pleura may be sutured as shown here.



Fig. 20-12. Following total left pneumonectomy, there was in this patient such an abundance of mediastinal pleura that complete covering of the hilar structures could be accomplished.

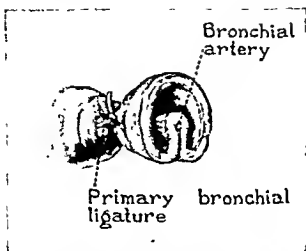


Fig. 20-15 Diagrammatic drawing illustrating the effect of a circumferential ligature of the bronchus. The primary encircling ligature produces an infolding of the posterior membranous portion. In some instances the latter is so abundant that the degree of compression demonstrated in this drawing under the encircling ligature cannot always be obtained.



Fig. 20-16 Roentgenogram of patient two hours after total left pneumonectomy. Attention is called to the extreme shifting of the mediastinum to the left side with elevation of the diaphragm. Shifting to the operative side must have resulted from immediate compensating dilatation of the remaining lung. (From W. F. Rienhoff, courtesy The Southern Medical Journal)



Fig. 20-17. Roentgenogram of the chest of a patient 2.5 years after total left pneumonectomy (following Lipiodol injection). Compensatory increase in the size of the right thoracic cavity and dilatation of the right lung are evident. The stump of the left primary bronchus is sharply defined. The trachea is deflected to the left. The left diaphragm is elevated. (From W. F. Rienhoff, courtesy The Southern Medical Journal)

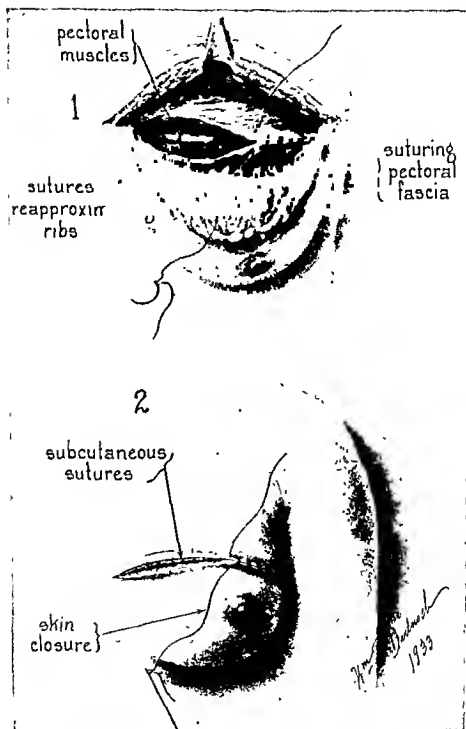


Fig 20-14 1 Shows the sutures for reapproximation of the ribs and the suturing of the pectoral fascia. 2. The fascia is drawn together with interrupted medium silk while the skin is closed with fine silk. (from W. F. Rienhoff and E. N. Broyles, courtesy Journal of the American Medical Association.)

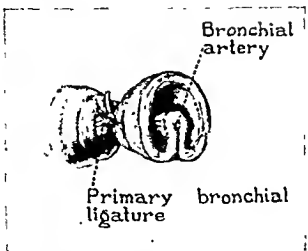


Fig. 20-15. Diagrammatic drawing illustrating the effect of a circumferential ligature of the bronchus. The primary encircling ligature produces an infolding of the posterior membranous portion. In some instances the latter is so abundant that the degree of compression demonstrated in this drawing under the encircling ligature cannot always be obtained



Fig. 20-16. Roentgenogram of patient two hours after total left pneumonectomy. Attention is called to the extreme shifting of the mediastinum to the left side with elevation of the diaphragm. Shifting to the operative side must have resulted from immediate compensating dilatation of the remaining lung (From W. F. Rienhoff, courtesy The Southern Medical Journal)



Fig. 20-17. Roentgenogram of the chest of a patient 25 years after total left pneumonectomy (following Lipiodol injection). Compensatory increase in the size of the right thoracic cavity and dilatation of the right lung are evident. The stump of the left primary bronchus is sharply defined. The trachea is deflected to the left. The left diaphragm is elevated. (From W. F. Rienhoff, courtesy The Southern Medical Journal)

with fine silk (Figure 20-14). In the female, it is usually necessary to suture the breast subcutaneously, the latter serving as a good tampon over the pectoral fascia. Within two weeks the wound has healed solidly and there is no impulse or bulging during coughing. No drainage is employed. A rather snug dressing is applied and the patient is returned to his room.

first or second step without jeopardizing the viability of the lung during the interval between operations. In this manner, the scope of usefulness of total pneumonectomy is sufficiently widened to deal with patients of various age groups and in different states of physical fitness.

Variations occur in the number and size of the bronchial arteries, depending upon cer-

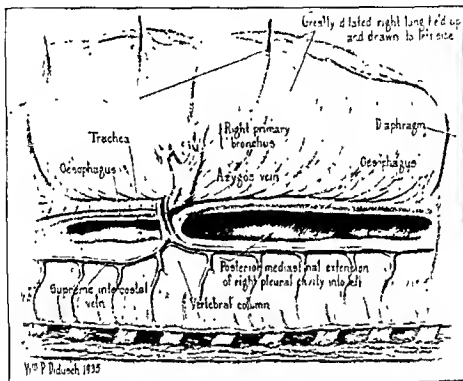


Fig. 20-18. Drawing made at autopsy of a patient who died six months after total left pneumonectomy. It shows enormous dilatation of the right lung. The shaded regions represent the burrowing of the posteromedial portion of the right upper, middle, and inferior lobes through the posterior mediastinum above and below the azygos vein. This depression extended inward for a distance of about 6 cm. (From W. F. Riehoff, courtesy *The Southern Medical Journal*)

DISCUSSION

Owing to the location of the new growth and the extent of the cancer in the majority of patients, total pneumonectomy is, except in most unusual instances, the ideal operation for the treatment of carcinoma of the lung. One-stage pneumonectomy is to be preferred when feasible, but graded pneumonectomy should be employed whenever the slightest doubt arises regarding the patient's safety. The steps to be taken in carrying out either one-stage or graded pneumonectomy are identical and have been described. The operation may be interrupted following either the

tam pathologic changes in the lung. The number and size of the bronchial arteries increase in carcinoma of the lung, probably because of the greater nutritional demands of the tumor. It has also been our clinical observation that the size of the pulmonary artery decreases in direct proportion to the extent of involvement of the lung by the tumor. The less the aerating ability of the lung parenchyma, the less blood will be carried by the pulmonary artery for oxygenation and, conversely, the more will be supplied by the bronchial arteries for maintenance of nutrition.

The restitutive compensatory mechanism

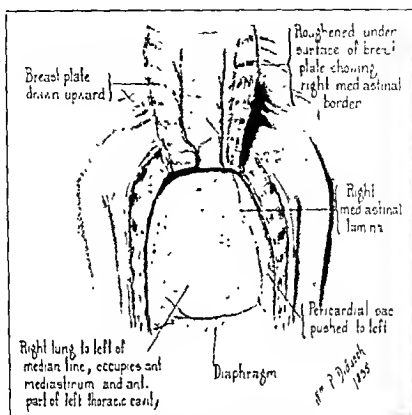


Fig. 20-19. Breast plate removed from the same patient as in Figure 20-18. This shows deflection of the mediastinal contents to the extreme left with the upper and middle lobes of the right lung bulging well over into the anterior mediastinum. (From W. F. Rienhoff, courtesy *The Southern Medical Journal*.)

following total or partial removal of a lung is based essentially on three factors: (1) the readjustment and adaptation of the thoracic cage and diaphragm on the side operated upon, as well as upon the side not operated upon; (2) the compensatory dilatation of the remaining lung; (3) the production of a space-occupying, fenestrated labyrinth of connective tissue which tends to fill the remain-

ing dead space, if any remains when factors (1) and (2), after their maximal restorative efforts, have failed to bring about a complete obliteration of the remaining thoracic space (Figures 20-16, 20-17, 20-18, and 20-19).

(See Chap. 18 for a discussion of the operability, operative mortality, and five-year survival rates of bronchogenic carcinoma.)

The Prone Position in Thoracic Surgery

**Richard H. Overholt
and
Wilford B. Neptune**

The prone position in thoracic surgery was originally developed on our service to prevent contralateral flooding during resection for suppurative lung disease. Other equally important advantages have been discovered which have made it our position of choice for most intrathoracic procedures that involve the lung or posterior mediastinum. Although familiarity with the technical problems associated with all approaches is desirable, one should use that position which is most advantageous from the standpoint, first, of the patient and then of the surgical team including the anesthetist. The slight inconvenience of the latter can well be sacrificed in the interest of the safety of the former. In our experience, the prone position with a liberal posterolateral approach best meets this objective.

ADVANTAGES OF THE PRONE POSITION PHYSIOLOGIC ADVANTAGES

An unrestrained contralateral costal arch, free diaphragmatic excursion, and absence of mediastinal sag permit ventilation of the contralateral lung without assistance. Therefore, constant positive intrabronchial pressure is not required. Sucking action of negative intrapleural pressure is maintained; and return flow of blood to the right heart is not adversely affected. Sustained assistance with pressure in the closed circuit is, therefore, purposefully avoided. The intrabronchial pressure is raised only to inflate segments as required in their testing and delineation in segmental resection; or in patients with low reserve.

Comparative studies have been done by

Beeches, Quinn, Bunker, and D'Alessandro [1] in patients having lobectomy or pneumonectomy in various positions. They found that elimination of carbon dioxide in the prone position *without assistance of respiration* was as good in the case of lobectomies and better in the case of pneumonectomies than in the lateral position with bag squeezing or machine assistance to respiration.

PREVENTION OF CONTRALATERAL FLOODING

The prone position is the most favorable of all for the natural drainage of bronchial secretions. Material that does not spontaneously flow out or is not expelled by coughing can be more easily reached by aspiration. Flooding of the contralateral lung is far less likely. The increased safety in regard to contralateral flooding is best exemplified by the report of Moore, Murphy, and Elrod [2] who noted an incidence of 14 per cent contralateral tuberculous spreads among patients having resection in the lateral position, as compared to a similar group having surgery performed during the same time interval and by the same surgical group with a 1.6 per cent contralateral spread in the prone position.

BETTER EXPOSURE

There is immediate access to the posterior mediastinum and pulmonary hilus which increases the ease of the subsequent hilar dissection. With a given amount of surgical exposure, no other position allows such ease in the management of a densely adherent lung or of a large, solid tumor.

TECHNICAL ADVANTAGES

The weight of the lung allows it to fall forward and out of the way, making the use of lung clamps and traction unnecessary. This, together with better exposure, allows greater ease in the handling of tissues.

In the event of hemorrhage, the blood drains away, thus permitting its control with greater ease. In the lateral position the hilus is at the base of the cavity and quickly becomes submerged in a pool of blood, mak-

ence to the endotracheal tube in particular. If it comes out, it may be difficult to reinsert in the prone position; therefore, it is the responsibility of the anesthesiologist to make certain that the endotracheal tube is properly and adequately fixed in position.

DISADVANTAGES TO THE OPERATING TEAM

It usually takes longer to open and close the thoracic cage, owing to the necessity of

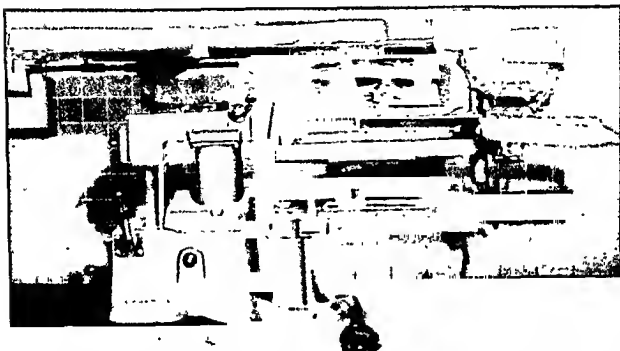


Fig 21-1. The Overholt-Comper thoracic table. The table has the following advantages. (1) Provision is made for lateral tilt in either direction (2) The pelvic girdle may be elevated or lowered independently of the shoulder and head supports. (3) The face, shoulder, arm, and pelvic supports are individually adjustable. (4) The entire table may be adjusted as to height from the floor (5) Wound-irrigating fluids are directed to a bucket by a removable drip pan. (This table was constructed by the American Sterilizer Company, Erie, Pennsylvania.)

ing subsequent control difficult and contralateral flooding a real danger.

TEACHING VALUE

In our experience, no other position is so favorable for observers, since the entire surgical field can be visualized from the lateral aspect of the operating table.

DISADVANTAGES OF THE PRONE POSITION

DISADVANTAGES TO THE ANESTHESIOLOGIST

There is less margin of safety in regard to any mistakes that may be made, with refer-

either cutting or removing at least one rib. In the lateral position, a simple intercostal incision will often suffice, taking advantage of the anterior mobility of the thoracic cage. In the prone position, however, the anterior extent of the incision cannot be utilized and, owing to the limited posterior mobility, one, two, or more ribs must be cut, or, if desired, removed. In our practice, we usually cut two ribs at their angle and these are then approximated by mortise-tenon joint repair during closure. (Figure 21-4.)

The second assistant, on the opposite side of the operating table, is in an uncomfortable position to observe and assist. Usually, how-

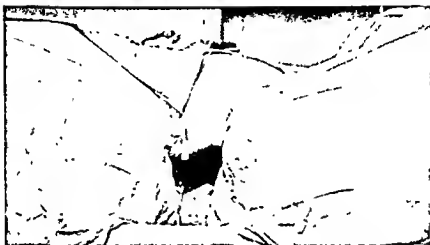


Fig 21-2. (Top) Patient in prone position for a right thoracotomy. (Bottom) The patient has been prepared and draped.

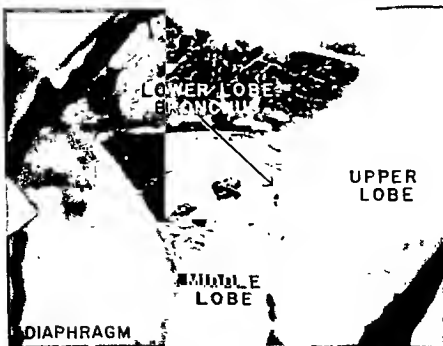


Fig. 21-3. View following resection of the right lower lobe, showing exposure obtained in the prone position.

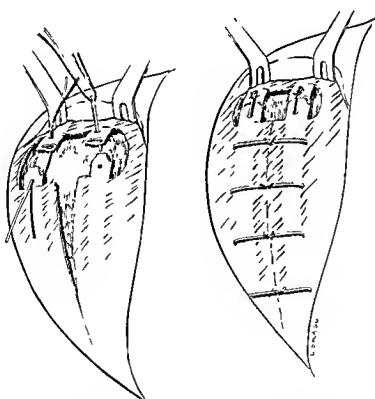
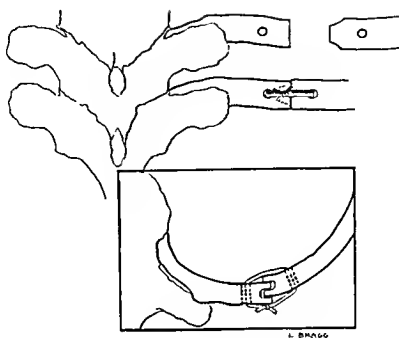


Fig 21-4. Drawings illustrating the technic of mortise-tenon joint repair of transected ribs during closure.

ever, one assistant is sufficient, owing to the technical advantages, and the second assistant need not remain on the opposite side except during the opening and closure.

CONTRAINDICATIONS TO THE PRONE POSITION

SUPERIOR VENA CAVAL OBSTRUCTION

Superior vena caval obstruction is an absolute contraindication to the prone position. As such, any tumor involving the upper mediastinum, as carcinoma of the right upper lobe, in particular, and associated with questionable caval occlusion, is considered carefully before being placed in the prone position and usually will be explored in the lateral position. In the prone position the shoulder support may, by the weight of the patient, produce pressure on the underlying tumor, with further compromise of the caval circulation. Occasionally, patients with narrow anteroposterior diameters of the upper thorax develop clinical evidence of caval obstruction when placed in the prone position, and they should be explored in the lateral or supine position.

THORACIC CAGE DEFORMITIES

Although uncommon, deformities such as severe kyphoscoliosis or pectus excavatum probably should not be placed in the prone position because of technical problems.

INFANTS

In general, owing to their small size, children of less than six years of age are difficult to suspend in the prone position.

PRECAUTIONS

The technical details are most easily managed if the patient has the endotracheal tube inserted under topical anesthesia and is allowed to help in assuming a position of comfort in regard to the head, shoulders, pelvis, arms, and legs. We usually do our bronchoscopic examination under topical anesthesia immediately before surgery. If there are no bronchoscopic contraindications to surgery, the tube is then inserted and the patient placed in the prone position while awake. General anesthesia is then induced. If for some reason the patient has general anesthesia prior

to insertion of the endotracheal tube, a light plane of anesthesia should be present when the patient is turned and placed in the prone position to prevent hypotension and/or cardiac irregularities. Such phenomena have been observed when the protective reflexes are abolished under a deep plane of anesthesia.

It is the surgeon's responsibility to make certain that the position is correct in regard to the head so as to prevent pressure on the eyes. Also, the shoulder girdle should be positioned so as to prevent any possible pressure on the brachial plexus, or obstruction to the venous return of the head and upper extremities. Most important of all, the upper chest support, when properly positioned, merely supports. If placed too low on the anterior thoracic wall, it tends to restrict thoracic excursion during breathing and the patient by necessity must elevate the entire body weight during inspiration.

Provision should be made for regulation of intrapleural pressures as the patient is returned to bed. During shift from the prone to the supine position there may be marked pressure changes in the pleural space. These sudden changes can best be managed by making certain that the pleural space contains a catheter connected to underwater-seal drainage to allow escape of air during closure of the thoracic cage and subsequent shift in position. Although such drainage is routine in all thoracotomies, it is especially important following pneumonectomy. In such cases the tube remains open until the patient has been returned to bed and then it is clamped, it is periodically reopened as needed for intrapleural pressure adjustment and removed on the second or third postoperative day.

COMMENT

The prone position provides advantages that increase the safety for the patient from the viewpoint of the anesthesiologist and the surgeon. It cannot and should not be used for all thoracic surgical procedures. One should choose a position that best suits the patient and suits best the surgery to be done. In our experience, the prone position, with a posterolateral approach, best serves this purpose in most cases needing pulmonary resection as well as many other thoracic procedures.

Treatment of Lung Tumors by Lobectomy and Pulmonary Segmental Resection

James C. Baldwin

The exact status of lobectomy in the treatment of pulmonary cancer is undetermined. Whereas pneumonectomy is the standard procedure for pulmonary cancer, many situations exist in which lobectomy or the even more conservative procedure of segmental resection should be performed. The lower mortality and the conservation of healthy pulmonary tissue are the major advantages of the more conservative operations. The question of whether the surgical compromise in not removing the entire lung harboring the neoplasm endangers the patient's chance for cure awaits determination. The reluctance to accept lobectomy as a method of treating pulmonary cancer is attested to by the fact that until recent years very few papers dealing with this subject had appeared in the English language (Effler [15], Belcher [4]; Robinson, Jones, and Meyer [22]). Nevertheless, lobectomy has been extensively practiced for the treatment of pulmonary cancer. Practically every article dealing with the surgical treatment of this neoplasm includes a report on patients subjected to lobectomy for cancer of the lung. Careful selection of the various operative procedures available to the patient with lung cancer and critical analysis of the accomplishments of the respective operations will demonstrate the exact position of the more conservative procedures. A given operation can thus be tailored to the specific needs of the patient.

INDICATIONS FOR LOBECTOMY

The indications for lobectomy are: (1) the establishment of the histologic nature of a lung lesion when routine measures have not been successful; (2) the resection of meta-

static tumors limited to a particular segment or lobe (Figure 22A-1) (see Chap. 24); (3) the excision of small, peripheral, primary bronchogenic carcinomas (Figure 22A-2) without evidence of spread to the hilar or mediastinal nodes (this is especially true in elderly patients, in whom the preservation of lung tissue for adequate pulmonary function is necessary); (4) as a palliative procedure for certain incurable bronchogenic carcinomas where peripheral pneumonia and lung abscess cause considerable disability; (5) the excision of benign tumors, such as bronchial adenomas, pulmonary adenomatosis, hamartomas, and fibromas; (6) the excision of certain inflammatory lesions (not discussed in this chapter).

Recently, radical lobectomy—namely, lobectomy coupled with hilar and mediastinal node dissection—has been advised for pulmonary carcinoma where preservation of lung tissue is essential for pulmonary function (see Chap. 22B).

SURGICAL ANATOMY

The Jackson-Huber [16] classification of the lung segments and, accordingly, segmental bronchi, segmental arteries, and, to a lesser extent, segmental veins, has been almost universally adopted (Figures 22A-3 and 22A-4). In this chapter, these structures will be considered in anatomic sequence, according to the surgical attack on each structure in the course of dissection for lobectomy or segmental resection.

Anatomy of the Pulmonary Arteries

The right and left pulmonary arteries lie anterior to the bronchus and superior to the

pulmonary vein in the region of the hilus of the lung (Figure 22A-5). The pulmonary arterial trunk is at least 5 cm. in length and twists as it arises to bifurcate into the right and left pulmonary arteries. Because this arching occurs around the ascending aorta to the left, the right pulmonary artery is longer than the left.

into two segmental pulmonary arteries: a superior branch to the apical segment, a second branch to the anterior segment, and occasionally a small second branch to the anterior segment of the right upper lobe.

A third branch of the pulmonary artery to the right upper lobe is usually present (according to Appleton [1] in 90 per cent of



Fig. 22A-1. (Left) A.P. tomograph of a female, thirty-four years old, showing two solitary, discrete nodules in the lower lobe of the left lung with no evidence of nodules elsewhere, metastatic from a primary melanoma of the shoulder removed elsewhere. (Right) Gross specimen of melanoma removed by lobectomy.

RIGHT PULMONARY ARTERY

The right pulmonary artery extends posterior to the ascending aorta, the superior vena cava, and the right pulmonary vein. It is anterior to the esophagus, and anterior and slightly inferior to the bronchus. It is superior and slightly inferior to the right superior pulmonary vein.

At the level of the bifurcation of the right upper-lobe bronchus, the right pulmonary artery bifurcates into the superior pulmonary trunk and the inferior pulmonary trunk.

Usually a common trunk enters the *right upper lobe* and almost immediately divides

cases). It is referred to as the posterior ascending branch, and may arise from the interlobar portion of the right pulmonary artery or from a common branch that divides to supply the posterior segment of the right upper lobe and the superior segment of the right lower lobe.

Variations in all these branches may be present. They may come off the arterial stem as single branches or as a common stem with three or four branches. A recurrent branch from the apical and anterior segmental arteries may run superior and posterior to the right upper-lobe bronchus to supply the pos-

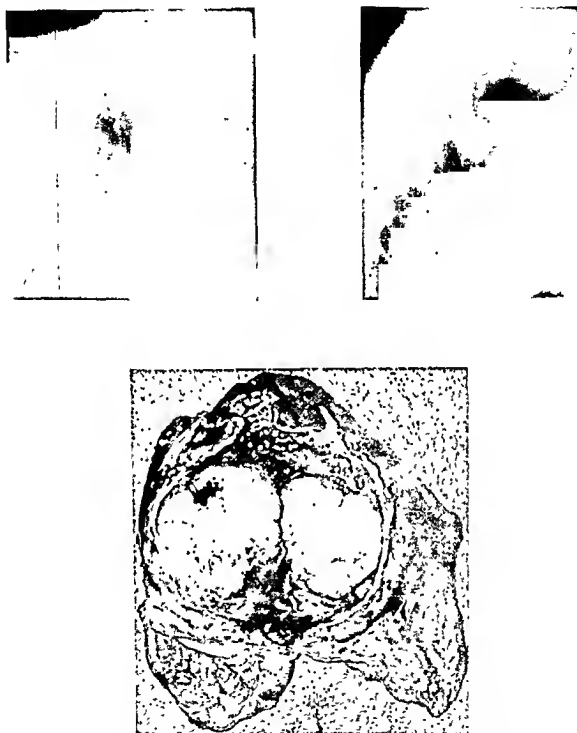


Fig 22A 2. Primary bronchiolar carcinoma of the upper lobe of the right lung in a sixty year-old male. (Top left) A P tomograph showing solitary round-cell focus peripherally in the right upper lobe. (Top right) Lateral tomograph confirming position. (Bottom) Gross specimen removed by lobectomy. Patient alive and well 55 years after lobectomy.

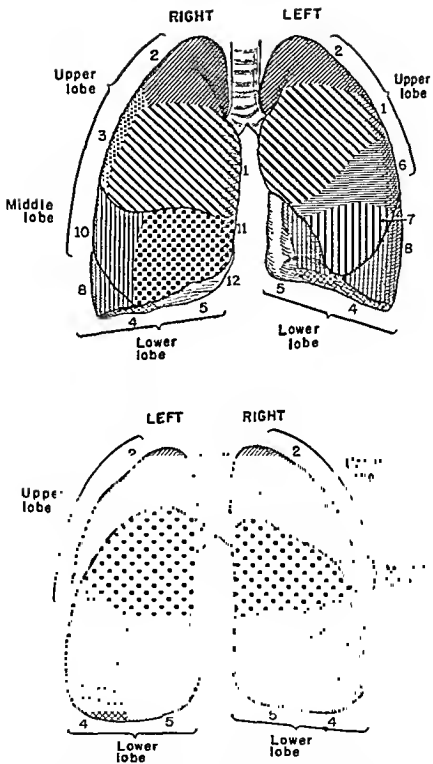


Fig. 22A-3. Diagrammatic drawings illustrating segmental divisions of the lungs, with an enlargement of hilar structures (Top) Anterior view, (Bottom) Posterior view.

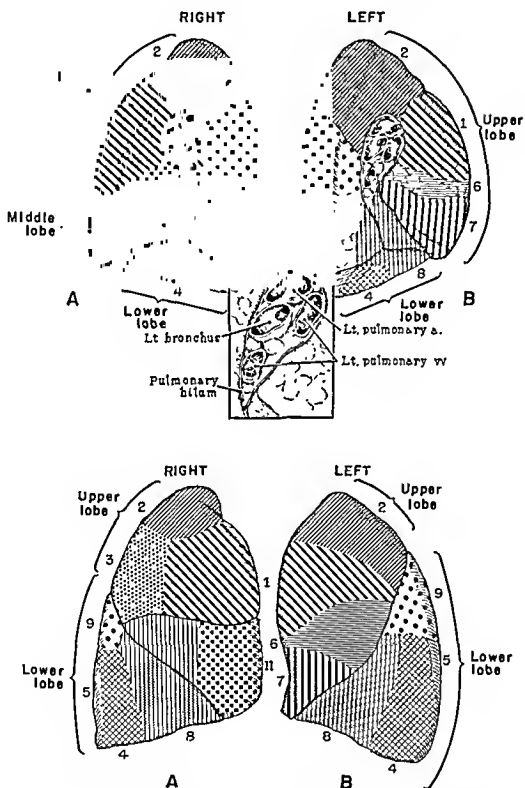


Fig 22A-4. Diagrammatic drawings illustrating segmental divisions of the lungs, with an enlargement of hilar structures. (Top) Medial view. (Bottom) Lateral view.

terior segment. Other variations may occur [2].

The *inferior pulmonary arterial trunk* supplies the right middle and lower lobes and often gives rise also to branches to the upper lobe. In the interlobar fissure, where it crosses the interlobar bronchus, it lies posterior to the superior pulmonary vein and its branches. The approach to this portion of the inferior pulmonary trunk is through the junction of

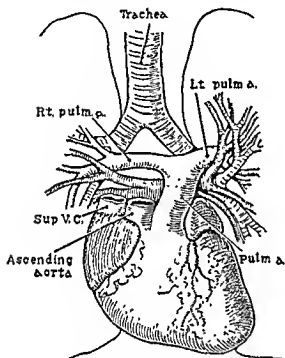


Fig 22A-5 Showing anatomic relations of the main pulmonary arteries, veins, and bronchi.

the oblique and horizontal fissure of the right lung. At this point there is present the bifurcation of all vessels to the lower and middle lobes. In the course of lobectomy or segmental resection, all must be seen and isolated prior to their ligation.

The arteries to the *right middle lobe* arise anteriorly and usually are two in number, one to each segment of the middle lobe. However, variations are often present in which a single trunk divides almost immediately into two or three branches, or into a small and a large branch, or into two large branches and one small branch. The superior branch usually supplies the medial segment and the inferior branch the lateral segment.

Arteries to the *right lower lobe* are usually five in number. A superior segmental artery

to the superior segment of the right lower lobe arises slightly inferior to the artery to the middle lobe and is posterolateral to it. As it arises in the depths of the interlobar fissure, it follows closely the bronchus to the superior segment. In dissection of this vessel, care should be taken to insure that the ascending branch to the posterior segment of the right upper lobe does not originate from a common trunk and is the only source of supply. Occasionally two small arteries supply the superior segment of the right lower lobe instead of a single large vessel.

The basilar segmental arteries arise slightly below the superior segmental artery and often bifurcate into an anterior and a posterior trunk which soon subdivide into four smaller branches. The anterior and medial branches from the anterior and the posterior trunk stem into the posterior and lateral segments. In the author's experience this has been found more common than four single arterial branches, each to its own segment. These vessels are anterior and anterolateral to the bronchi to the lower lobe.

LEFT PULMONARY ARTERY

The left pulmonary artery is relatively short. It extends anterior to the descending aorta and vagus nerves and loops over the left main-stem bronchus. The superior pulmonary vein is caudad to the artery.

Arteries to the *left upper lobe* supply the apical posterior segment, anterior segment, and lingular segments. As in the right lung, variations in the number and arrangement of these vessels are the rule rather than the exception. These have been seen as one or two trunks that immediately bifurcate into branches, or as five or six separate branches originating directly from the main artery.

The first branch arises from the superior portion of the left pulmonary artery as it crosses the main-stem bronchus. Usually a very short trunk is present prior to the division into branches: the apical branch superiorly and a posterior branch posterior and slightly inferior to the apical branch.

The anterior segmental branch usually arises as a primary vessel of the left pulmonary artery and runs anteriorly over the bronchus to the upper lobe. It may arise as a separate branch from the common trunk

with lingular segmental arteries in the interlobar portion of the left pulmonary artery, posterior and inferior to the upper-lobe bronchus, or as a single artery directly from the interlobar artery.

The lingular segmental arteries arise as a common stem, or as two separate arteries lying close together, from the interlobar portion of the left pulmonary artery. These branches arise as the artery crosses the lower-lobe bronchus in the interlobar fissure, and on the anterosuperior surface.

The superior segmental artery to the *left lower lobe* arises posterior and inferior to the lingular segmental branches and anterior to the bronchus. Soon after the branching of the lingular segmental arteries to the upper lobe, the basilar segmental arteries branch and follow the bronchi closely. These likewise may occur as two trunks, dividing into four segmental branches, or they may occur as four separate segmental branches.

Anatomy of the Pulmonary Veins

The pulmonary veins generally defy pattern identification. The bizarre nature of the number of branches, the regions collected, and the number of trunks and divisions vary widely. Each case must be treated individually, with care taken to isolate the branches to a particular segment or lobe according to the findings on careful dissection of all branches prior to ligation.

Several generalities can be made as a guide. There are two major systems of veins: (1) the subpleural, and (2) the intersegmental, which lie between the segmental planes. The subpleural veins course beneath the visceral pleura and collect, with the intersegmental, at the base of the segments, uniting with other segmental veins to form trunks prior to entry into the main superior or inferior pulmonary vein. Communications between these veins lie in the interlobar fissures and between segments in the intersegmental plane. The relationships of the main pulmonary veins are the most important consideration.

RIGHT SUPERIOR PULMONARY VEIN

The right superior pulmonary vein lies anterior to the trunk of the pulmonary artery and inferior to the right upper-lobe artery and passes posteriorly to the superior vena

cava. It collects from all segments of the upper and middle lobes of the right lung.

There are often three main trunks from the *right upper lobe* entering the superior pulmonary vein, two coursing superficially beneath the pleura and one deep in the substance of the lung. The superficial division collects from (1) the apical and anterior segments; (2) the posterior portion of the anterior segment, drained by a branch superficially from the undersurface of the interlobar fissure. The deep division collects from the intersegmental planes between the apical and anterior segments, and the apical posterior segments; and when it enters the right superior vein it lies posteriorly, being hidden by the other two branches.

The veins of the *right middle lobe* enter the superior pulmonary vein as a trunk or as separate branches, but usually are distinct from those of the upper lobe and enter the superior pulmonary vein at its inferior portion.

RIGHT INFERIOR PULMONARY VEIN

The right inferior pulmonary vein lies posterior and inferior to the superior pulmonary vein. Whereas the superior pulmonary vein lies beneath the pleura and is easily identified, the inferior pulmonary vein lies in the central portion of the hilus. It has a very short stump and empties directly into the auricle. Usually two distinct divisions are present: one, the superior segment of the right lower lobe, and the other, the basilar segment of the right lower lobe. The first may consist of one to three branches and enter posteriorly to the bronchus. It is easily identified when the right lower lobe is reflected anteriorly. The basilar segmental veins can arise as two trunks, or as three to six separate veins that enter into the inferior pulmonary vein.

LEFT SUPERIOR PULMONARY VEIN

This is formed by the vessels draining the *left upper lobe*, comparable with the right upper and right middle lobes. Its anatomic relationships are similar to those of the right superior pulmonary vein, lying anterior and inferior to the left pulmonary artery and the bronchi. There are usually distinct divisions between the trunks from the apical posterior segments and the anterior segments and that

from the lingular segments. There are three or four branches from the apical posterior and anterior segments; these are more superficial than those on the right side.

LEFT INFERIOR PULMONARY VEIN

The left inferior pulmonary vein lies in a position similar to that of the right, being central in location and inferior. It usually differs from the right in being comparatively long and, therefore, is more easily secured. As with the right vein, collection is from the lower lobe, usually by two distinct trunks, one from the superior segment of the left lower lobe and the other from the basilar segment of the left lower lobe.

The Bronchial Arteries and Veins

There are usually four types of bronchial arteries, and their number varies from one to four on each side.

On the right side, there is a single bronchial artery in approximately two thirds of instances, and a duplicated bronchial artery in one third; on the left side, approximately two thirds have duplicated arteries and one third a single bronchial artery. When there are two, the upper is the superior and extends on the anterosuperior surface of the bronchus, while the inferior is on the posteroinferior portion of the bronchus.

On the right side, the origin is from the intercostal branch stem in conjunction with the first aortic intercostal artery. On the left, the bronchial artery arises from the anterior surface of the thoracic aorta and in approximately 15 per cent of cases arises directly from the arch of the aorta on the concave side. In 10 per cent of cases, the left bronchial artery arises from the first intercostal bronchial artery.

On both sides, the artery is retropleural. On the right side, it runs deep to the arch of the azygos vein, while on the left it runs deep to the hemiazygos vein.

Most of the venous return is via the pulmonary vein, although bronchial veins do occur and usually empty into the azygos and hemiazygos systems.

Anatomy of the Bronchi

The trachea is 10 cm. long, descending from C6 to D5 thoracic vertebrae, and bi-

furcates into the right main-stem bronchus and the left main-stem bronchus in varying anatomic patterns.

RIGHT MAIN-STEM BRONCHUS

The right main-stem bronchus is shorter, wider, and more vertical than the left, and divides into three branches.

The bronchus to the *right upper lobe* arises approximately 2.5 cm. below the bifurcation. It is usually short and bifurcates almost immediately into the three segmental bronchi—apical, anterior, and posterior—that extend to their particular segments.

The bronchus to the *right middle lobe* arises 1 to 1.5 cm. below the orifice of the right upper lobe and is situated anteriorly. It also is relatively short, averaging 1 cm. before dividing into the medial and lateral segmental bronchi.

The bronchus to the *right lower lobe* is difficult to term a bronchus, because the superior segmental bronchus arises almost directly opposite the middle-lobe orifice and often slightly superiorly. Thus, when a lower-lobe lobectomy is performed, it is frequently necessary to ligate this segmental bronchus separately, and then the basilar segmental bronchi are transected. To include all segments would of necessity injure or obstruct the middle-lobe bronchus.

The basilar segmental bronchi often branch into two and then four divisions—the medial, lateral, anterior, and posterior—and run accordingly.

LEFT MAIN-STEM BRONCHUS

The left main-stem bronchus is much narrower and longer than the right. It passes caudad to the aortic arch, anterior to the esophagus and the descending thoracic aorta.

The bronchus to the *left upper lobe* arises approximately 5 cm. from the bifurcation. Almost immediately it subdivides into two main divisions: (1) the apical posterior and anterior segments, and (2) the lingular segments. The first division almost immediately subdivides into two or three segmental bronchi, with two of these going to the apical posterior segments and the third to the anterior segment. The second division, to the lingular segments, likewise descends and di-

vides into the superior and the inferior segmental bronchi.

The bronchus to the *left lower lobe* usually follows the same course and pattern as on the right side, with the superior segmental bronchus about 0.5 cm. inferior to the level of the upper-lobe orifice.

The basilar segmental bronchi follow the same course as on the right side. However, on the left side it is often easier to transect the lower-lobe bronchus to include the superior segment and the basilar segments, without injury to the division of the upper lobe supplying the apical posterior, anterior, and lingular segments.

TECHNIQS OF LOBECTOMY

The approaches to the chest cavity are described in Chapters 20 and 21. The technics discussed here are via the posterolateral approach, the one usually favored by the author.

The following surgical dictums apply to the performance of any lobectomy.

1. The closure of the severed bronchus by interrupted suture technic has proved most successful. Encircling sutures tend to cut off the blood supply to the stump, with resultant slough and fistula. The blood supply to the bronchus runs longitudinally, and interrupted sutures are likewise longitudinal. The shorter the stump, the less the chance of puddling of sputum, but care must always be taken to prevent compromising other segments or the main bronchus.

2. Care should be taken not to ligate the bronchial arteries too far distal to the line of closure of the bronchus.

3. Extrapleuralization, if technically possible, helps seal off the stump. Usually a portion of the pleura can be sutured over the bronchus with a few interrupted sutures.

Right Upper Lobectomy

With the lobe deflated and retracted inferiorly and posteriorly, and using the azygos vein as a guide, the pleura is carefully dissected from the hilus of the upper lobe. The artery is located, lying anteriorly and superiorly, and is dissected free. The ease and safety of the operation are enhanced when the entire pulmonary artery and its bifurcation into the right stem are in direct view. Two ligatures of 00 silk are then placed about

the artery proximally and distally and the artery transected, leaving a long proximal stump.

With all arterial branches isolated and secured, the superior pulmonary vein is dissected in a similar manner, care being taken to isolate only the veins draining the upper lobe—that is, the three venous tributaries—and carefully preserving the veins to the middle lobe.

The lobe is retracted superiorly, to open the interlobar fissure at the horizontal and oblique fissures and expose the posterior ascending segmental artery. If these fissures are fused, a retrograde dissection is safer, following the course of the division of the bronchus.

The bronchus is dissected superiorly, starting about the inferior portion of the upper-lobe bronchus, after which it is clamped distally. Two silk sutures are placed through the bronchus anteriorly and posteriorly, and the bronchus is cut approximately 4 to 5 mm. from the bifurcation. The bronchial stump is closed with interrupted sutures of atraumatic 000 silk, the sutures being placed approximately 2 to 3 mm. apart.

Should the fissures be incomplete, the bronchus is retracted superiorly and anteriorly, and with the lower and middle lobes inflated the line of demarcation is seen. Using traction and with the index or middle finger of the left hand placed in the line of demarcation on the pleural surface, the small venous connections are readily seen and can be clamped and severed. The posterior ascending branch of the artery comes into direct view in the course of the dissection and can be isolated, ligated, and transected.

Right Middle Lobectomy

The approach for right middle lobectomy is by dissection in the oblique fissure, which is almost always well developed. If the horizontal fissure is also well formed, it can be separated to expose the interlobar portion of the pulmonary artery. All arterial branches are isolated, including the superior segmental branch of the lower lobe, the segmental artery to the basilar segment of the lower lobe, the posterior ascending branch to the posterior segment of the right lobe, and the segmental branches of the middle lobe. The segmental

from the lingular segments. There are three or four branches from the apical posterior and anterior segments; these are more superficial than those on the right side.

LEFT INFERIOR PULMONARY VEIN

The left inferior pulmonary vein lies in a position similar to that of the right, being central in location and inferior. It usually differs from the right in being comparatively long and, therefore, is more easily secured. As with the right vein, collection is from the lower lobe, usually by two distinct trunks, one from the superior segment of the left lower lobe and the other from the basilar segment of the left lower lobe.

The Bronchial Arteries and Veins

There are usually four types of bronchial arteries, and their number varies from one to four on each side.

On the right side, there is a single bronchial artery in approximately two thirds of instances, and a duplicated bronchial artery in one third; on the left side, approximately two thirds have duplicated arteries and one third a single bronchial artery. When there are two, the upper is the superior and extends on the anterosuperior surface of the bronchus, while the inferior is on the posteroinferior portion of the bronchus.

On the right side, the origin is from the intercostal branch stem in conjunction with the first aortic intercostal artery. On the left, the bronchial artery arises from the anterior surface of the thoracic aorta and in approximately 15 per cent of cases arises directly from the arch of the aorta on the concave side. In 10 per cent of cases, the left bronchial artery arises from the first intercostal bronchial artery.

On both sides, the artery is retropleural. On the right side, it runs deep to the arch of the azygos vein, while on the left it runs deep to the hemiazygos vein.

Most of the venous return is via the pulmonary vein, although bronchial veins do occur and usually empty into the azygos and hemiazygos systems.

Anatomy of the Bronchi

The trachea is 10 cm. long, descending from C6 to D5 thoracic vertebrae, and bi-

furcates into the right main-stem bronchus and the left main-stem bronchus in varying anatomic patterns.

RIGHT MAIN-STEM BRONCHUS

The right main-stem bronchus is shorter, wider, and more vertical than the left, and divides into three branches.

The bronchus to the *right upper lobe* arises approximately 2.5 cm. below the bifurcation. It is usually short and bifurcates almost immediately into the three segmental bronchi—apical, anterior, and posterior—that extend to their particular segments.

The bronchus to the *right middle lobe* arises 1 to 1.5 cm. below the orifice of the right upper lobe and is situated anteriorly. It also is relatively short, averaging 1 cm. before dividing into the medial and lateral segmental bronchi.

The bronchus to the *right lower lobe* is difficult to term a bronchus, because the superior segmental bronchus arises almost directly opposite the middle-lobe orifice and often slightly superiorly. Thus, when a lower-lobe lobectomy is performed, it is frequently necessary to ligate this segmental bronchus separately, and then the basilar segmental bronchi are transected. To include all segments would of necessity injure or obstruct the middle-lobe bronchus.

The basilar segmental bronchi often branch into two and then four divisions—the medial, lateral, anterior, and posterior—and run accordingly.

LEFT MAIN-STEM BRONCHUS

The left main-stem bronchus is much narrower and longer than the right. It passes caudad to the aortic arch, anterior to the esophagus and the descending thoracic aorta.

The bronchus to the *left upper lobe* arises approximately 5 cm. from the bifurcation. Almost immediately it subdivides into two main divisions: (1) the apical posterior and anterior segments, and (2) the lingular segments. The first division almost immediately subdivides into two or three segmental bronchi, with two of these going to the apical posterior segments and the third to the anterior segment. The second division, to the lingular segments, likewise descends and di-

possible to transect the bronchi to the lower lobe as one bronchus; but if doubt exists regarding the origin of the lingular segmental bronchus, it is preferable to dissect the superior segmental bronchus separately and then the basilar segmental bronchi.

INDICATIONS FOR PULMONARY SEGMENTAL RESECTION

Pulmonary disease frequently tends to be limited to lung segments that can be removed successfully by segmental resection.

section, with preservation of lung tissue. Contralateral disease in the form of metastatic cancer or bronchiectasis may be treated by this method.

Segmental resection is not indicated for bronchiogenic carcinoma except as a palliative procedure.

TECHNIC OF PULMONARY SEGMENTAL RESECTION

The technic used is that devised by Doctors J. M. Chamberlain and Robert Klop-

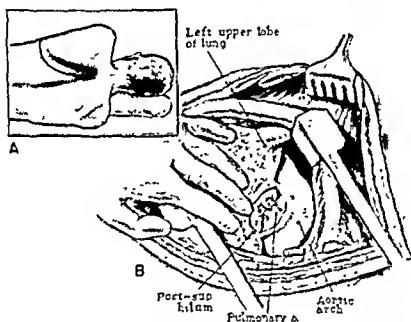


Fig. 22A-6. Resection of the left apical posterior segment of the left upper lobe. A. Incision used B. Showing division of the pulmonary arterial branches.

Tuberculosis often can be surgically treated by a segmental resection or removal of the feeding focus of the disease.

Bronchiectasis is a segmental disease. Mainly, the basilar segments of the right lower lobe, the middle lobe, and the lingular segments of the left upper lobe and the basilar segments of the left lower lobe are involved, whereas the superior segments of the lower lobe and the upper lobe are often free of disease.

Solitary cysts, benign tumors such as fibromas, chondromas, hamartomas, hemangiomas, and arteriovenous fistulas, and tumors metastatic to the lung may be segmental in distribution and removable by segmental re-

section [10] and is based on the studies of Churchill, Blades, Clagett, and Overholt, along with the basic contributions of Boyden, Scannell, and Appleton.

The same technic is followed in all segments, applying the anatomic relationships previously described (Figures 22A-6, 22A-7, 22A-8, and 22A-9).

The segmental artery is identified and divided first (Figure 22A-6), unless there is danger of contamination, in which case an attempt is made to isolate the bronchus first and clamp it to prevent spillage.

The segmental vein, particularly that on the pleural surface of the segment, is located and divided (Figure 22A-7).

branches to the middle lobe are then dissected free, ligated, and transected. The middle-lobe bronchus is thus brought into view.

The middle lobe is next retracted posteriorly and inferiorly until the superior pulmonary vein is located and the branch from the middle lobe carefully isolated, ligated, and transected.

The middle-lobe bronchus is located, isolated, and transected, and the stump closed as described for the upper-lobe bronchus.

The fissures are next transected. If the horizontal fissure is incomplete, the same technic as described for incomplete fissure in the right upper lobe is used, except that the middle-lobe bronchus is retracted anteriorly and superiorly with the upper lobe and lower lobe inflated; and with traction against the index or middle finger, the intercommunicating veins and bronchials are severed and ligated.

Right Lower Lobectomy

The approach is similar to that for middle-lobe lobectomy. After dissection and direct visualization of the middle-lobe arteries, the superior segmental artery to the right lower lobe and the posterior ascending artery to the right upper lobe, the artery to the superior segment of the right lower lobe is dissected free, severed, and ligated. The basilar segmental arteries are then isolated and ligated.

Next, the lobe is raised superiorly and the inferior pulmonary ligament divided. Small vessels are often present and require ligation in the inferior pulmonary ligament. As the division of the pulmonary ligaments is performed, the inferior portion of the inferior pulmonary vein is seen. Frequently it is preferable to ligate the vein from the superior segment separately. The venous trunk on the right side is very short, and it is expedient to ligate the branches rather than the trunk itself, and thus prevent possible slipping of the ligatures.

The bronchi are next carefully exposed and the middle-lobe bronchus is isolated. As stated previously, it is desirable to dissect the superior segmental bronchus separately and then the basilar segments. Should this dissection be performed too high, encroachment on and collapse of the middle lobe will occur.

Left Upper Lobectomy

The first step is the anterior and inferior displacement of the lobe and incision of the mediastinal pleura over the pulmonary artery. The anterior arterial branch and the apical and posterior segmental branches, whether arising as a single trunk or as individual branches, are each doubly ligated and transected. The apical posterior branch of the vein often obstructs exposure of the anterior segmental artery, and it is ligated prior to visualization of the artery. The pleura is then opened in the fissure along the length of the main pulmonary artery. The branches to the lingular segments are located in the fissure, extending anteriorly and inferiorly, and are treated as the other branches.

The superior pulmonary vein is next located by displacing the lobe posteriorly and inferiorly. Dissection from a proximal position, extending distally, exposes the branches without danger of rupture at the bifurcation. All tributaries are isolated and treated separately.

The bronchus to the left upper lobe is now approached from the superior and posterior position, where the pulmonary artery can be carefully observed and avoided at all times. Again, transection is carried out about 1.5 to 1.0 cm. from the bifurcation, and the bronchus is closed with interrupted atraumatic silk sutures.

Left Lower Lobectomy

As on the right side, the interlobar fissure is opened first and all vessels, including the superior segmental branch to the lower lobe, the lingular segmental arteries, and the basilar segmental arteries, are visualized prior to their severance. The superior segmental artery is then transected and ligated. If a single artery remains below the lingular arteries, this may be transected as one stem or, if not, as separate vessels.

The inferior pulmonary vein is approached by dividing the inferior pulmonary ligament. The posterior mediastinal pleura is divided, and then the vein to the superior segment is divided. The basilar segmental veins are often better transected individually.

The bronchi are approached through the interlobar fissure. On the left side, it is often

and drawn down over the raw surface and sutured in place. Care should be taken to preserve the intersegmental vein, as this supplies also the segments inferior to the resected tissue.

RESULTS OF CONSERVATIVE RESECTION OF LUNG TUMORS

Lobectomy and segmental resection are the operative procedures of choice for any benign tumor of the lung that can be totally resected. The rationale for lobectomy for bronchogenic carcinoma awaits evaluation; however, more and more authors are reporting

may, of course, be due to careful selection of patients.

Belcher analyzed the accomplishments of lobectomy for bronchial carcinoma as performed by a number of British surgeons. He stated that of the 264 patients reported on, 12 died postoperatively; of 156 operated upon two or more years ago, 50 per cent survived; of 96 operated upon three or more years ago, 48 per cent survived; of 46 operated upon four or more years ago, 55 per cent survived, and of 18 operated upon five or more years ago, 61 per cent survived. Of the 119 patients who died, 47 per cent died of generalized

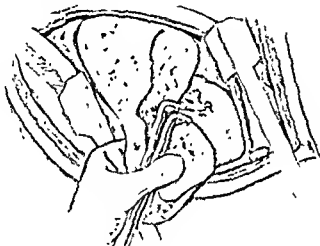


Fig 22A 9 Pulmonary segmental resection. Illustrating position of hands for dissection of segmental plane

a lower mortality and higher five-year survival rates, and are shifting to conservative resection.

Many authors have reported on the utilization of lobectomy in the treatment of bronchogenic carcinoma (Boyd, Smedal, Kirtland, Kelley, and Trump [7], 32 cases; Sellar [23], 86 cases; Bignall and Moon [5], 74 cases; Watson [24], 16 cases; Belcher [4], 264 cases; Churchill, Sweet, Scannell, and Wilkins [12], 93 cases; Rienhoff, King, and Dana [21], 46 cases; Burford, Ferguson, and Spjut [9], 74 cases).

Most of the authors who have reported their experience with lobectomy indicate that this procedure carries with it a much lower mortality than does pneumonectomy and that the results of the procedure are good. This

metastases, 23 per cent of local metastases, 10 per cent from the operation, and 16 per cent from causes other than cancer. Belcher calls attention to the fact that the series of patients analyzed by him may represent a group in whom the tumor was diagnosed early and while still localized, as was indicated by the fact that only 27 per cent of the patients presented evidence of metastases to regional lymph nodes.

In contrast to this figure is a series reported by Bignall and Moon [5], in which metastases to lymph nodes occurred in 58 per cent of the patients. These authors reported that when metastasis to lymph nodes had occurred, there was a 16 per cent five-year survival of patients subjected to pneumonectomy and, surprisingly, a 25 per cent five-

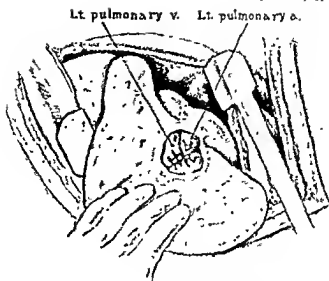


Fig. 22A-7. Pulmonary segmental resection. Arteries ligated, venous branches to the segment tied.

The segmental bronchus is then located, circumscribed, and clamped distally. Following this, inflation of the lung is performed to assure the ligation of the correct bronchus, which is then transected, with proximal closure (Figure 22A-8).

The lung is expanded, outlining clearly the segment being removed. Traction is now applied to the bronchus. The surgeon's hands are then placed so that the pleural surface of the hilus is approximated between the index

finger anteriorly and the thumb posteriorly (Figure 22A-9). Gentle dissection is performed with the thumb until a venous channel or cross-communicating bronchus is encountered, at which time it is clamped with mosquito clamps and severed. This permits further dissection, which is always performed from the hilus distally to the periphery. The pleura is next excised. If pleura is required for extrapleuralization of the raw surface, it can be stripped off the lung tissue with ease

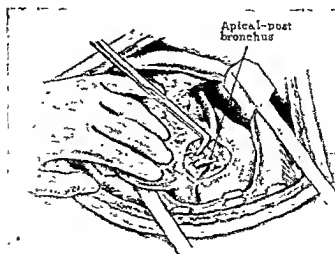


Fig. 22A-8. Pulmonary segmental resection. Arteries and veins have been tied, resected. Segmented bronchus is isolated and clamped.

Radical Lobectomy in the Treatment of Lung Cancer

William G. Cahan

The term "lobectomy" has usually been used by physicians without a qualifying adjective. For better definition, more specific terms should be employed. For the sake of clarity, a *simple* lobectomy is defined as an operation restricted to the excision of a lobe, or lobes, alone. A *radical* lobectomy is an operation in which one or two lobes of a lung are excised in a block dissection with their regional hilar and mediastinal lymphatics and lymph nodes. This chapter will discuss the indications for and technic of radical lobectomy.

The adjective "radical" is patterned after its use to qualify other surgical procedures for cancer and implies the addition of a specific, reasonably well-defined block lymphatic dissection to organ removal. It does not infer an operation of great magnitude in which adjacent thoracic structures, such as chest wall or diaphragm, are added to the excised organ. When these are included as part of excisional surgery, they are defined in specific terms; for example, "a right upper lobe radical lobectomy with excision of ribs 3, 4, and 5," or, "a middle and lower lobe simple lobectomy with partial pericardiectomy."

RATIONALE

The desirability of removing a malignant tumor en bloc with its regional lymphatic drainage region is an established principle of cancer surgery when certain circumstances exist:

1. No metastases are discernible in sites or numbers considered to be lethal; e.g., supraclavicular lymph nodes in lung cancer or multiple liver metastases in colon cancer.

2. No other form of therapy has curative value.

3. The morbidity and mortality rates of the necessary surgical procedure remain reasonably low.

4. From experience, a high index of probability exists for present or future involvement by cancer of the lymphatic pathways and lymph nodes to be excised.

5. If these lymphatics and their lymph nodes are not resected at the time of the original procedure, they would be hidden within the body so that their future involvement by metastases would escape early detection.

This concept provides the basis for the traditional treatment of cancers arising in the colon, stomach, breast, and other organs. It is also the principle upon which "radical pneumonectomy" [5] is founded (see Chap. 19).

Metastases to lymph nodes occur in a large percentage of patients with lung cancer. One of the earliest large-scale analyses was by Ochsner [17] who reported that in 3,047 collected cases of cancer of the lung, 72.2 per cent of the regional lymph nodes were found to be involved, and that prognosis is dependent upon the presence of such metastases. Nohl studied in detail, by special technics, the lymphatics removed at the time of pulmonary surgery. He found an 88.8 per cent lymph node involvement where radical pneumonectomies had been carried out. The incidence after radical lobectomy was 41.4 per cent. The over-all involvement of lymph nodes in 100 resected specimens was 75 per cent. (See Chap. 23 for additional discussion of evidence of metastases to lymph nodes

year survival of patients subjected to lobectomy. When metastasis to lymph nodes had not occurred, pneumonectomy produced a 49 per cent five-year survival rate and lobectomy a 47 per cent five-year survival rate. In this series, therefore, lobectomy produced results as good as and in fact better than did pneumonectomy. During the years 1950 and 1951 no patient in Bignall and Moon's series died subsequent to lobectomy, as compared to a 13 per cent mortality rate following pneumonectomy.

Aufses reported that from 1935 to 1947 at Mount Sinai Hospital (New York) 86 patients survived operation, of whom 52 had pneumonectomy and 34 lobectomy; 17 patients who underwent pneumonectomy and 13 patients (38 per cent) who underwent lobectomy for pulmonary cancer survived five or more years.

Churchill, Sweet, Seannell, and Wilkins [12], reporting from the Massachusetts General Hospital, stated that in 127 pneumonectomies performed for bronchial carcinoma between 1948 and 1956 the mortality rate was 10 per cent, and in 93 lobectomies performed during the same period the mortality rate was 6.4 per cent. The five-year survival rate for the 127 patients subjected to pneumonectomy was 24 per cent; somewhat less than the 33 per cent survival obtained for the 93 patients who underwent lobectomy. These authors call attention to the enormous number of variables in attempting to define the number and location of metastases to regional lymph nodes. However, as a clinical measure in accepting the statement of the pathologist who examined the specimens in a "routine manner" the following results obtained: for 56 patients who underwent pneumonectomy between 1948 and 1953 and who had metastases to regional lymph nodes, the five-year survival was 16 per cent, and for 28 patients with "negative nodes" the five-year survival

was 46 per cent; for 15 patients with metastases to lymph nodes who underwent lobectomy, the five-year survival was 20 per cent, and for 43 patients without evidence of metastases to lymph nodes, the five-year survival was 35 per cent.

Burford, Ferguson, and Spjut [9], reporting from the Barnes Hospital (St. Louis), stated that pneumonectomy is the preferred procedure for all cell types except bronchiolar carcinoma, for which lobectomy is favored. Of their 356 resectable cases, 79.3 per cent were treated by pneumonectomy, 20.2 per cent by lobectomy, and 0.5 per cent by segmental resection. The percentage of lobectomies has been steadily increasing despite their stated preference for pneumonectomy; in 1948 lobectomies comprised only 3.3 per cent of their total resections, whereas in 1955 the percentage had increased to 29.5 per cent. They attribute the rise to the extended use of lobectomy in palliation and in older patients with borderline respiratory reserve, and to its use in selected cases of small peripheral tumors. The mortality rate of their series was 8.8 per cent of 247 patients subjected to exploration alone; 13 per cent of 280 patients subjected to pneumonectomy; and 12 per cent of 74 patients subjected to lobectomy.

Richard H. Meade, through the co-operation of Sir Clement Price Thomas in London, studied the autopsy findings of 73 patients who died an average of twenty months after resection of their cancers. In the 23 patients in whom lobectomy was performed, there was no evidence of local recurrence in 26 per cent; metastases in the ipsilateral lymph nodes were encountered in 21 per cent; and there was no recurrence in the pericardium [19].

Accordingly, lobectomy is curing a significant number of patients with bronchogenic carcinoma while leaving them with normal respiratory function.

chains and a few inconstant retrotracheal nodes.

Right Paratracheal Nodes

The paratracheal nodes are placed in a niche, the boundary of which is as follows: in the front, the superior vena cava and the right innominate vein; behind, the right anterolateral surface of the trachea; medially, the arch of the aorta and the innominate artery; above, the right subclavian artery surrounded by the right recurrent nerve; below, the arch of the vena azygos; laterally, the niche is closed by that part of the mediastinal pleura which extends from the superior vena cava and the right innominate vein to the right lateral border of the trachea, and which is skirted by the vagus nerve.

The right paratracheal chain consists of three to six nodes which may be arranged in a single file, although most of these are in groups of two to three in juxtaposition. The chain is not truly vertical but bends somewhat posteriorly. The highest node is at the same time the most laterally placed and the most posterior, and is often remarkable for its size, particularly when it receives a large lymphatic trunk coming from the nodes at the bifurcation. It rests immediately below the right subclavian artery but may insinuate itself partly behind this vessel. Above this node arise the nodes of the right recurrent chain. Generally, the lowest node of this right paratracheal chain is the largest and is always found at the arch of the vena azygos, which in the majority of cases covers its lower pole, or actually the node may project over this vein. It has been called the "node of the arch of the vena azygos" (the azygos vein node).

Afferent and efferent lymphatics in this group form a very important ascending right paratracheal lymphatic path, which is a continuation of the vessels that issue from the right lung, the right suprabronchial and retrobronchial nodes, and from the nodes of the bifurcation. This path also receives directly some lymphatic vessels from the trachea, the esophagus, and the thymus gland. It terminates above either in the right lymphatic duct or in a separate entrance into the jugulosubclavian angle.

Left Paratracheal Nodes

The left paratracheal chain consists of four or five nodes placed along the anterior and medial aspects of the vertical segment of the left recurrent nerve, occupying a position along the recurrent nerve lateral to the left posterolateral border of the trachea, medial to the pleura, and medial and posterior to the arch of the aorta and the left subclavian artery. They ascend in the left paratracheal lymphatic path.

The retrotracheal nodes are placed behind the inferior part of the trachea on the path of the lymphatic vessels that unite the subcarinal nodes to the right paratracheal chain. These are present in about one eighth of the cases. Generally there is but one node placed a little above the tracheobronchial angle near the right border of the posterior surface of the trachea along the esophagus and the vagus nerve.

SUBCARINAL NODES (NODES OF THE TRACHEAL BIFURCATION)

This group occupies the interval between the trachea formed by the divisions of its two bronchi and above the inferior pulmonary veins. There are usually three to five nodes, which are fused in such a way as to have a mammiliform shape, indicating an incomplete division of this node into smaller elements. The total number of elements in it varies. These nodes are in contact with the inferior border of the trachea and the suprajacent bronchus. They even extend somewhat in front of the tracheal spur, and there is a bond of union between the subcarinal nodes and the inferior extremities of the paratracheal chain. They are in relation with the pericardium in front and with the esophagus, vena azygos, and aorta behind. The efferent lymphatics from these nodes usually proceed to the right paratracheal chain (rarely to the left paratracheal chain), and reach their destination and pass either in front of or behind the tracheobronchial tree.

NODES OF THE PULMONARY ROOTS

A group of nodes is placed between the elements that make up the pulmonary root. They are listed as anterior, posterior, superior,

and its effect upon prognosis.)

At the Memorial Center there are eleven patients operated on five or more years ago who have lived without recurrence after radical pneumonectomy and whose specimens showed evidence of metastatic cancer in lymph nodes. The types of cancer in this group were: eight epidermoid carcinomas, one adenocarcinoma, one terminal bronchiolar carcinoma, and one malignant bronchial adenoma.

It can be seen, therefore, that prolongation of life has been effected largely by the excision of the extrapulmonically placed lymph nodes as part of the operation for pulmonary cancer, and there is an important prognostic value derived from an analysis of the contents of such nodes.

We have added resection of hilar and mediastinal lymph nodes to pulmonary resection as a part of radical pneumonectomy. It seemed logical to explore the value of such an addition to a lobectomy. For a better understanding of radical lobectomy, an anatomic and physiologic description of pulmonary lymphatic drainage follows.

LYMPHATIC SYSTEM OF THE LUNG

No article on lymph node drainage should begin without a tribute to the excellent studies of Rouvière [18], and it is strongly recommended that his original work be consulted for a more detailed and thorough account than that which follows and which was derived liberally from it.

Rouvière points out that even as there are different anatomic features to the contents of the right and left thoracic cavities, so are there variations in the lymph node pattern and drainage on both sides. He defines several major divisions of node-bearing regions: mediastinal, tracheobronchial, and intrapulmonary.

MEDIASTINAL LYMPH NODES

The *anterior mediastinal* or prevascular nodes are placed in the superior portion of the mediastinum in front of the large blood vessels, which are connected with the heart. On the right side, the chain is placed in front of the superior vena cava and the right innominate vein in a prevenous location with

one prominent node at the junction of both innominate veins. Lymph nodes about the right phrenic nerve and inferior vena cava also drain into this pathway, terminating at the right jugulosubclavian junction or the right lymphatic duct.

The left anterior mediastinal chain is prearterial, or, more exactly, preaorticocarotid. It commences in a node of good size placed just in front of the ligamentum arteriosum, which rests on the left pulmonary artery. The left anterior mediastinal chain (preaorticocarotid) ascends between the phrenic and the vagus nerves, following chiefly the course of the latter nerve. The nodes of this chain are placed from below upward, at first in front of and on the superior border of the aortic arch, then above this vessel on the anterolateral surface of the common carotid artery. Often a few nodes are placed somewhat medially along or a little in front of the right lateral border of the thymus gland. The left lymphatic mediastinal path terminates in the thoracic duct or directly into the jugulosubclavian venous junction.

The transverse anterior mediastinal chain nodes are placed along the superior and inferior borders of the left innominate vein and may form an anastomosis between the right and left mediastinal pathways, as well as between the right and left paratracheal chain of nodes.

The *posterior mediastinal* nodes are juxtaesophageal. Normally two to five nodes are placed along the lateral borders of the esophagus at the level or somewhat below the inferior pulmonary vein and occasionally between the esophagus and the aorta. The greater number of the efferent vessels from these pour their contents into the subcarinal (intertracheobronchial) nodes while the rest empty into the thoracic duct. These can be grouped for purposes of simplicity with the pre-esophageal group described later.

TRACHEOBRONCHIAL LYMPH NODES

These include the paratracheal nodes, subcarinal nodes (or nodes of the bifurcation), and the nodes of the pulmonary roots. Two principal chains of nodes are present: the right and the left lateral or paratracheal

chains and a few inconstant retrotracheal nodes.

Right Paratracheal Nodes

The paratracheal nodes are placed in a niche, the boundary of which is as follows: in the front, the superior vena cava and the right innominate vein; behind, the right anterolateral surface of the trachea; medially, the arch of the aorta and the innominate artery; above, the right subclavian artery surrounded by the right recurrent nerve; below, the arch of the vena azygos; laterally, the niche is closed by that part of the mediastinal pleura which extends from the superior vena cava and the right innominate vein to the right lateral border of the trachea, and which is skirted by the vagus nerve.

The right paratracheal chain consists of three to six nodes which may be arranged in a single file, although most of these are in groups of two to three in juxtaposition. The chain is not truly vertical but bends somewhat posteriorly. The highest node is at the same time the most laterally placed and the most posterior, and is often remarkable for its size, particularly when it receives a large lymphatic trunk coming from the nodes at the bifurcation. It rests immediately below the right subclavian artery but may insinuate itself partly behind this vessel. Above this node arise the nodes of the right recurrent chain. Generally, the lowest node of this right paratracheal chain is the largest and is always found at the arch of the vena azygos, which in the majority of cases covers its lower pole, or actually the node may project over this vein. It has been called the "node of the arch of the vena azygos" (the azygos vein node).

Afferent and efferent lymphatics in this group form a very important ascending right paratracheal lymphatic path, which is a continuation of the vessels that issue from the right lung, the right suprabronchial and retrobronchial nodes, and from the nodes of the bifurcation. This path also receives directly some lymphatic vessels from the trachea, the esophagus, and the thymus gland. It terminates above either in the right lymphatic duct or in a separate entrance into the jugulosubclavian angle.

Left Paratracheal Nodes

The left paratracheal chain consists of four or five nodes placed along the anterior and medial aspects of the vertical segment of the left recurrent nerve, occupying a position along the recurrent nerve lateral to the left posterolateral border of the trachea, medial to the pleura, and medial and posterior to the arch of the aorta and the left subclavian artery. They ascend in the left paratracheal lymphatic path.

The retrotracheal nodes are placed behind the inferior part of the trachea on the path of the lymphatic vessels that unite the subcarinal nodes to the right paratracheal chain. These are present in about one eighth of the cases. Generally there is but one node placed a little above the tracheobronchial angle near the right border of the posterior surface of the trachea along the esophagus and the vagus nerve.

SUBCARINAL NODES (NODES OF THE TRACHEAL BIFURCATION)

This group occupies the interval between the trachea formed by the divisions of its two bronchi and above the inferior pulmonary veins. There are usually three to five nodes, which are fused in such a way as to have a mammiliform shape, indicating an incomplete division of this node into smaller elements. The total number of elements in it varies. These nodes are in contact with the inferior border of the trachea and the suprajacent bronchus. They even extend somewhat in front of the tracheal spur, and there is a bond of union between the subcarinal nodes and the inferior extremities of the paratracheal chain. They are in relation with the pericardium in front and with the esophagus, vena azygos, and aorta behind. The efferent lymphatics from these nodes usually proceed to the right paratracheal chain (rarely to the left paratracheal chain), and reach their destination and pass either in front of or behind the tracheobronchial tree.

NODES OF THE PULMONARY ROOTS

A group of nodes is placed between the elements that make up the pulmonary root. They are listed as anterior, posterior, superior,

and inferior, according to their position and relation to the respective bronchus. They are present, if anterior, in prevenous, prearterial, and prebronchial locations. The posterior nodes are found more frequently on the right side than on the left. The superior nodes, about one to three in number, are found most often on the left side, and lie along the superior border of the bronchus and behind the left pulmonary artery. This chain is constant and continuous above with the lateral

more often on the left than on the right side (the latter in only 20 per cent of the cases according to Rouvière). These drain to the subcarinal nodes (cf. above, posterior mediastinal nodes) and can drain to the infradiaphragmatic region as well.

INTRAPULMONARY NODES

Nodes are placed along the bronchoarterial trees of each lobe, and it is important to note that the principal node draining one lobe

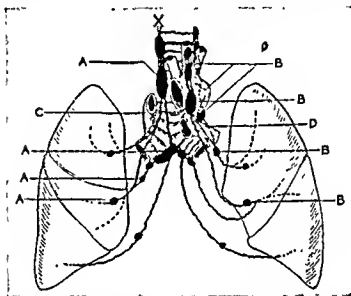


Fig 22B-1. Diagram illustrating lymphatic drainage of the lungs, divided into superior, middle, and inferior regions. The right lung, A, drains entirely up the right lymphatic pathway. The lower two segments of the left lung, lower B, drain predominantly to the subcarinal nodes and then up the right lymphatic pathway. Occasionally they may also travel up the left lymphatic pathway, joining the drainage from the superior section of the left lung, upper B. (Note that the sections are not confined by major fissures) C. Azygos major vein. O. Pulmonary artery. (From Drinker [11], after Rouvière.)

tracheal, left recurrent chain of nodes by means of a lymphatic vessel that passes below the arch of the aorta and the ligamentum arteriosum (Figure 22B-16). There is a node of the loop of the left recurrent nerve at this level. Arnstein attributes certain cases of paralysis of the left recurrent nerve to tuberculosis of these lymph nodes. This might also be true when metastases are present that burst the nodal capsule and invade the nerve secondarily.

The pre-esophageal nodes of the inferior pulmonary ligament extend from just below the bronchus to the diaphragm, and are found

group may rest against the bronchus of an adjacent lobe.

Each lung has three principal lymphatic regions: superior, middle, and inferior (Figure 22B-1). These are *not* limited by the usual anatomic boundaries or major fissures. In fact, when there is incomplete separation of lobes from each other, interlobar lymphatics follow the communicating vascular channels.

Right Lung

The superior lymphatic region is represented by the anteromedial portion of its upper lobe. Its collecting vessels are tributaries

solely of the right paratracheal nodes, particularly of the node of the arch of the vena azygos. The middle lymphatic region, which includes the posterolateral region of the upper lobe, all the middle lobe, and the superior part of the lower lobe, conveys lymph to both the right lateral tracheal and subcarinal nodes. The inferior lymphatic region comprises the inferior region of the lower lobe; the lymph

region includes the inferior region of the upper lobe as well as the superior and middle regions of the lower lobe. The vessels terminate in part superiorly in the anterior mediastinal and left paratracheal nodes, and in part inferiorly in the subcarinal nodes. The inferior lymphatic region represented by the inferior part of the lower lobe drains to the subcarinal nodes.

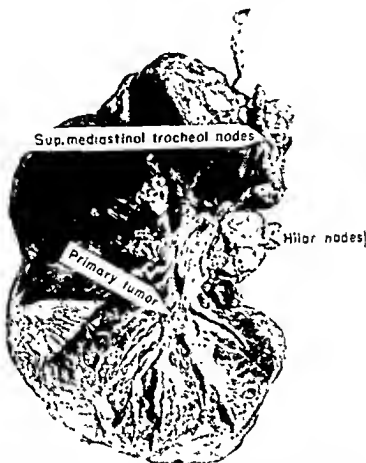


Fig 225 2. Right radical pneumonectomy specimen showing primary carcinoma of the right lower lobe with metastases to the subcarinal ("hilar") and paratracheal ("superior mediastinal tracheal nodes") lymph nodes

from this region is poured almost entirely into the subcarinal nodes.

Left Lung

The superior lymphatic region is comprised of the superior region of its upper lobe, the lymph-collecting vessels of this connect with the left paratracheal chain, the node of the ductus arteriosus with the left anteromedial nodes, and with the node of the loop of the left recurrent nerve. The middle lymphatic

Since the subcarinal nodes normally convey their efferent lymphatic trunks to the right paratracheal group, it follows that only the superior lymphatic region of the left lung in its entirety and the middle region of the same lung in part divert most of their lymph into the anterior mediastinal and left paratracheal nodes, and thence into the left jugulosubclavian venous confluence. With this knowledge, it might seem possible to foretell to some degree by which lymphatic route cancer

might progress, the site of which in the lung has previously been established. However, a carcinoma of the left upper lobe undoubtedly could cross lymphatic regions so that it may send metastases not only to the paratracheal and subaortic nodes but also to the subcarinal group as well [16].

LYMPHATIC DRAINAGE OF THE LUNG

Confirmation of Rouvière's dissection and deductions is found in Drinker's [11] report (Figure 22B-1). He cannulized separately the right lymphatic and the thoracic ducts in

firmation. It has been noted that lymph nodes containing metastatic lung cancer located in the right supraclavicular region just behind the clavicular head of the sternocleidomastoid muscle can be traced not only to carcinomas having their origin in the right lung, but also to cancers in the middle and lower lymphatic regions of the left lung. In fact, one may speculate that cancers of the lower two lymphatic regions of the left lung will have a poorer prognosis than do those of the right lung, because the contralateral placement of communicating lymph nodes will preclude



Fig. 22B-3 Right radical pneumonectomy specimen with metal tags to label different nodal levels for identification by the pathologists

dogs. Carbon particles were then deposited carefully by bronchoscope in various segments of the lung and their reappearance in the lymph flow of the right or left cannulas was noted.

As might be anticipated from Rouvière's work, when the particles were placed in any segment of the right lung or in the lower two-thirds of the left lung, the lymph emerging from the right cannula ("x" in Figure 22B-1) was colored by them, while that from the thoracic duct remained clear. Only when particles were deposited in the superior portion of the left upper lobe did they appear in the lymph issuing from the left cannula.

These experiments have found clinical con-

firmation. It has been noted that lymph nodes containing metastatic lung cancer located in the right supraclavicular region just behind the clavicular head of the sternocleidomastoid muscle can be traced not only to carcinomas having their origin in the right lung, but also to cancers in the middle and lower lymphatic regions of the left lung. In fact, one may speculate that cancers of the lower two lymphatic regions of the left lung will have a poorer prognosis than do those of the right lung, because the contralateral placement of communicating lymph nodes will preclude

their inclusion in a block dissection should they contain metastases. These pathways have been graphically demonstrated by the use of dyes according to the technique of Weinberg [20] (Chap. 19).

Specimens removed by radical pneumonectomy and radical lobectomy with their lymph node groups intact and clearly marked so as to maintain their relative position will aid further in delineating the pattern of metastatic spread [16] (Figures 22B-2 and 22B-3).

A careful study of lymph node involvement by metastases from autopsy specimens of patients who have died of lung cancer has provided a real aid in determining the flight of metastases [15]. In this connection, Cra-

foord [10] reported in his early articles at least three autopsies on patients who had had what was probably a simple pneumonectomy that revealed metastatic cancer in residual lymph nodes located in the paratracheal regions.

To be sure, variations in the pathways described above occur. In particular, metastasis from the lower two thirds of the left lung may

TECHNIC OF RADICAL LOBECTOMY

In the description of the technique to follow, emphasis is placed upon the method of lymph node dissection. The ligation and division of the tributary vessels and the bronchi to the various lobes are not included. These features are discussed in Chapter 22A.

In keeping with the tradition of starting a block dissection for cancer, the first step of

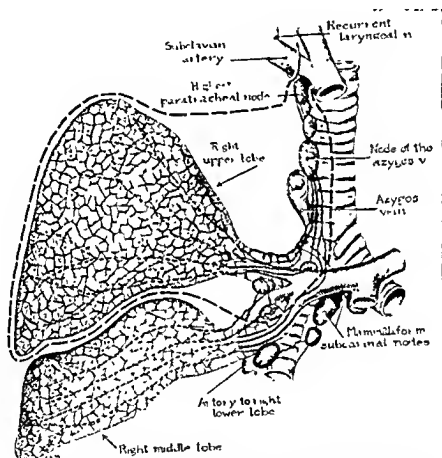


Fig 22B-4. Right upper lobe radical lobectomy, anterior view. Limit of excision indicated by broken line. Note inclusion of nodes along the intermediate bronchus and the important azygos vein node. Stump of right lower lobe bronchus shown, lobe omitted for clarity. (From W. G. Cahon, courtesy *Journal of Thoracic Surgery*.)

travel directly up the left side instead of by the more usual contralateral spread. In addition, with the choking of one node by metastasis, retrograde extension along pathways not ordinarily taken does occur. Skipping of lymph nodes by metastases has also been noted. By and large, however, metastases probably progress according to the routes outlined above.

each radical lobectomy ideally proceeds from the most distal region of potential spread and works back toward the hilus and the tumor. However, this cannot always be achieved, because adhesions and many other conditions in the thorax can obliterate clear anatomic planes. Instead of starting with the lymphatic dissection it may be necessary to begin at the hilus of the lobes by entering their fissures

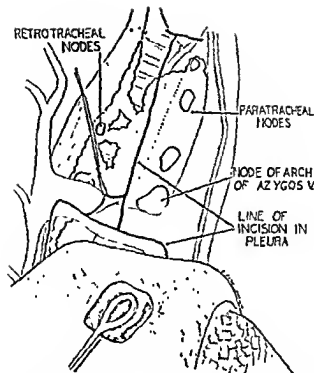


Fig 22B-5. Right upper lobe radical lobectomy. Right side: paratracheal lymph nodes. Heavy line indicates line of pleural incision.

and proceeding distalward, or using a combination of these techniques. Another technical variant may be indicated when the tumor invades the chest wall. It may be difficult to

approach the hilus until this extension or peripheral fixation is mobilized.

To approach either lung, the patient is placed in a true lateral position. This is preferred to the supine or prone position, for it provides an optimum exposure for mediastinal lymph node dissection. The chest is entered through a long, parascapular incision and the bed of the fifth or sixth rib. The pathologic setting is assessed, and if a radical lobectomy seems indicated and feasible, and the patient's general condition is satisfactory, the procedure is carried out.

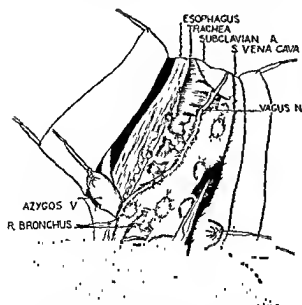


Fig. 22B-6. Right upper lobe radical lobectomy. Pleural flaps elevated, azygos vein divided. Dissection begun beneath superior vena cava.

Right Upper Lobe Radical Lobectomy

A right upper lobe radical lobectomy (Figure 22B-4) begins with the incision of the superior mediastinal pleura (Figure 22B-5) from the apex of the chest to the azygos vein arch just anterior to the vagus nerve. Superiorly, a short horizontal limb is used to facilitate exposure of the subclavian artery and right recurrent laryngeal nerve.

For the paratracheal dissection, the anterior pleural flap is elevated to the anterolateral surface of the superior vena cava, the phrenic

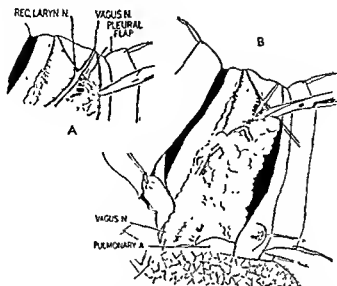


Fig. 22B-7. Right upper lobe radical lobectomy. Right side. A Apex of dissection beneath right subclavian artery. Note identification of right recurrent laryngeal nerve B, Vagus nerve distal to the recurrent laryngeal branch is divided. Note clearing of retrocaval space.

nerve being displaced with it (Figure 22B-6)*. The superior flap is mobilized as far as the vertebral bodies, leaving the vagus nerve uncovered. These flaps are retracted by the weight of hemostats fastened to sutures attached to their free edges.

The azygos vein is transected between ties and ligatures and the anterior limb lifted forward, thereby elevating the superior vena cava to some extent. The areolar tissue is cleared laterally and posteriorly from the superior vena cava, from the apex of the chest to an area just beneath the azygos vein junction with it. The upper thoracic portion of the vagus nerve is mobilized and the take-off of the right recurrent laryngeal branch is identified. The vagus is transected just distal to that point. This facilitates a clearer dissection of the paratracheal areolar tissue (Figure 22B-7).

The apex of the dissection is the inferior border of the subclavian artery where a tongue of areolar, node-bearing tissue is isolated and divided.

*Although there are lymph nodes lying in the periphrenic regions as well as anterior to the superior vena cava and innominate veins, these nodes have not been included, for they lie beyond the arbitrary limits of the dissection as suggested by the superior vena cava. It was also thought that the route of lymphatic spread on the right side was predominantly paratracheal and retrocaval to the jugulosubclavian junction.

Next, attention is directed to the trachea. The fine connective tissue on its right lateral and anterior surfaces is found to separate readily, allowing the whole packet of tissue anterior to the trachea to be swept downward

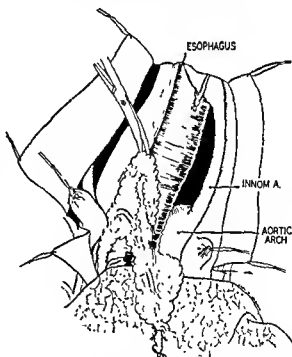


Fig. 22B-8. Right upper lobe radical lobectomy. Right side. Retrotracheal lymph node dissection. Note the most constant node at the tracheobronchial angle; also the boundaries of the retrocaval space.

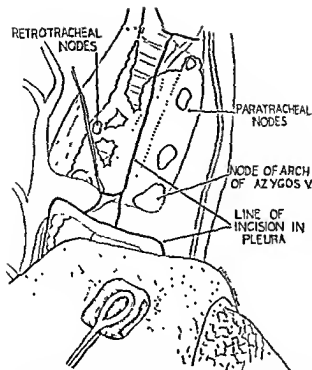


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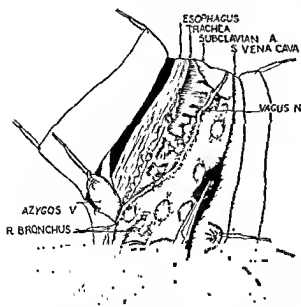


Fig. 22B-6. Right upper lobe radical lobectomy. Pleural flaps elevated, azygos vein divided. Dissection begun beneath superior vena cava.

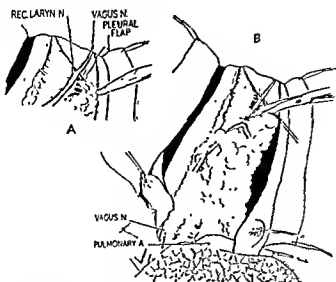


Fig. 22B-7. Right upper lobe radical lobectomy. Right side: A. Apex of dissection beneath right subclavian artery. Note identification of right recurrent laryngeal nerve. B. Vagus nerve distal to the recurrent laryngeal branch is divided. Note clearing of retrocaval space.

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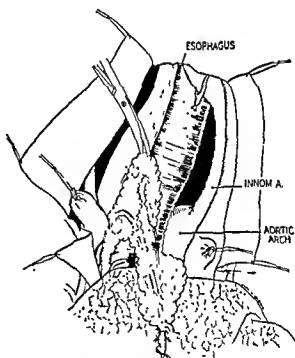


Fig. 22B-8. Right upper lobe radical lobectomy. Right side. Retrotracheal lymph node dissection. Note the most constant node at the tracheobronchial angle, also the boundaries of the retrocaval space.

off the innominate artery and aortic arch to the level of the pulmonary artery (Figure 22B-8). This can usually be done with division of only a few small vessels. This packet of tissue represents the right paratracheal

and on the esophagus (Figure 22B-8) is then freed from these structures, commencing superiorly, and dissected downward. Included in this dissection is the particularly important, constant, large node of the azygos arch lying

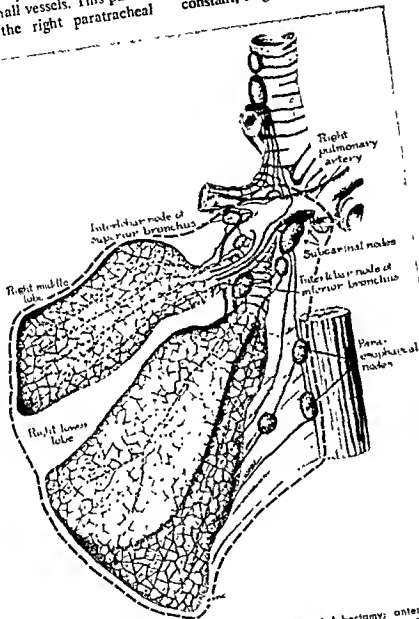


Fig. 22B-9. Right middle and lower lobe radical lobectomy; anterior view showing line of excision. Note inclusion of pre-esophageal, subcarinal, and interbranchial nodes. Paratracheal chain may be removed as a separate specimen. (From W. G. Cohen [5], courtesy *American Journal of Surgery*)

lymph node chain. To maintain the integrity of this block of lymphatics, the dissection must be carried immediately adjacent to the large vessels and the trachea.*

The areolar tissue posterior to the trachea

* In order to accelerate the dissection of the small vessels in the mediastinum, silver brain clips (McKenzie) are used for hemostasis instead of ligatures.

just above the pulmonary artery. It is the one most frequently involved by cancers of the right upper lobe. This node is mobilized as the dense connective tissue superior to the pulmonary artery and behind the superior vena cava is incised. This paratracheal node packet remains attached to the lung by peribronchial lymphatics and areolar tissue. As

each packet of nodes is mobilized, it should be tacked (Figure 22B-8) to a convenient point on the visceral pleura to keep it from obscuring the later dissection.

An incision is then made in the interlobar fissure separating the upper lobe from the

arterial trees of each lobe, and it is important to note that the principal lymph node draining one lobe group may rest against the bronchus of an adjacent lobe. The continuation of the right main-stem bronchus to form the middle and lower lobe bronchi (intermedi-

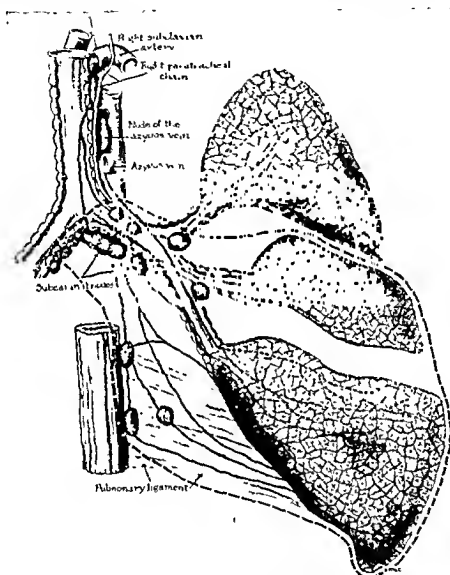


Fig 22B-10 Right middle and lower lobe radical lobectomy; posterior view. (From W. G. Cahan, courtesy *Journal of Thoracic Surgery*)

middle and lower lobes and carried down to the origin of the right upper lobe bronchus. A group of nodes can be found surrounding the main-stem bronchus. The posterior nodes of this group are found near the anterior edge of the esophagus on the right. On the left, they are less frequently found. These are dissected toward the specimen.

Lymph nodes are placed along the broncho-

ate bronchus) can be traced and it is usually feasible, and indeed of decided importance, to include the nodes that present themselves adjacent to these structures. These are nodes that Borrie [2] described as being in the "sump" position, and usually represent the lowermost site of spread from right upper lobe cancers. The division of the upper lobe bronchus can be helpful in providing a more

area along the intermediate bronchus can be obtained.

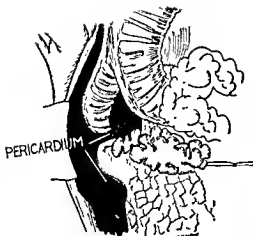


Fig. 22B-11 Right side: subcarinal lymph nodes dissected onto lung from both bronchi and pericardium. Esophagus retracted posteriorly. (From W. G. Cohan, W. L. Watson, and J. L. Pool [7], courtesy Journal of Thoracic Surgery)

thorough dissection of the retrocaaval and peribronchial nodes.

It is necessary, on occasion, in the treatment of cancers of the right upper lobe, to include the middle lobe as part of the block dissection. Such a bilobectomy is usually performed for the following three reasons: (1) when there is a partial to almost total symphysis of these two lobes; (2) when the tumor transgresses one lobe and is fixed to or invades the other; (3) when it is believed that a more complete dissection of the "sump"

Middle Lobe Radical Lobectomy
It is improbable that the middle lobe would be removed by itself if cancer were suspected except in the most unusual circumstances, such as in very poor-risk patients. Tumors within it are almost always excised in combination with a right upper lobe radical lobectomy. To such a bilobectomy are added not only all the nodes in the "sump" area, but as many as are available about the origin of the adjacent lower lobe bronchus as well.

At all times the indications for one operation or another are subject to flexibility and depend to a large extent upon the intrathoracic setting. For example, should the tumor extend between the middle and lower lobes, a lower lobe radical lobectomy en bloc with the middle lobe may be performed (Figure 22B-9), leaving the right upper lobe intact. However, the lymph node dissection of the upper mediastinal and paratracheal nodes, including the azygos node, may then be done separately.

Right Lower Lobe Radical Lobectomy

In a right lower lobe radical lobectomy (Figures 22B-9 and 22B-10), a procedure in which a middle lobe usually is included, dissection is

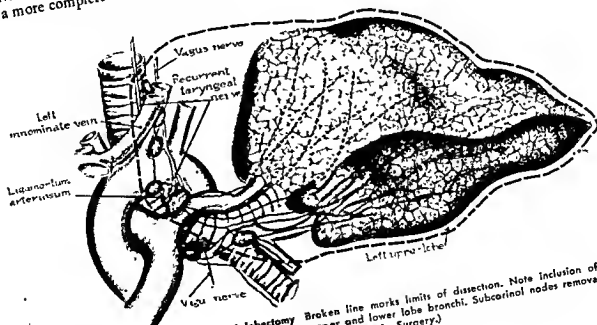


Fig. 22B-12. Left upper lobe radical lobectomy. Broken line marks limits of dissection. Note inclusion of inter-bronchial lymph node ("sump" position) between upper and lower lobe bronchi. Subcarinal nodes removed as a separate pocket. (From W. G. Cohan, courtesy Journal of Thoracic Surgery.)

begun at the diaphragm, with a division between ligatures of the inferior pulmonary ligament. The esophagus is identified and the areolar and lymphatic tissue along its anterolateral surface is elevated upward as far as the inferior pulmonary vein and tacked to the lower lobe. Steady, gentle traction on the lower lobe in an anterior direction will expose the subcarinal node packet. At this level this will become more available if the esophagus is

origin of the right upper lobe bronchus is identified and the nodes are taken from the intermediate bronchus and reflected toward the specimen. After identifying the right middle and lower lobe bronchi, their transection at this time will permit the inclusion of the more cryptically placed nodes about the origin of the right middle lobe bronchus. The division of the tributary arteries and veins to these two lobes can then be made.

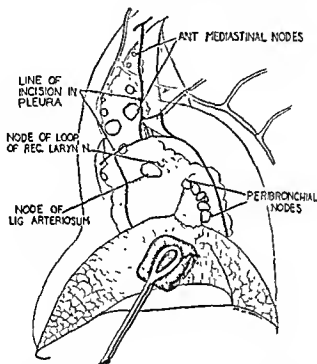


Fig 22B-13 Left upper lobe radical lobectomy. Left side, anatomy of anterior mediastinal and subaortic lymph nodes. The pleural incision is outlined.

retracted sharply posteriorly (Figure 22B-11). The inferior and medial edge of the subcarinal packet is usually easily dissected from the adjacent pericardium. It is not believed necessary, as some authors advocate [3], routinely to excise a portion of the pericardium with this packet, for only the most filamentous areolar connective tissue lies between this lymph node group and the pericardium. By entering the plane adjacent to the posterior edges of the left, of contralateral bronchial cartilages (Figure 22B-11), simple and practically avascular mobilization of this nodal packet is effected.

Dissection is then carried to the main stem bronchus, exposing its posterior surface. The

Left Upper Lobe Radical Lobectomy

For a left upper lobe radical lobectomy (Figure 22B-12) incision is made into the mediastinal pleura, beginning at the apex of the chest and proceeding along the vagus nerve to the arch of the aorta (Figure 22B-13). Its posterior limb follows the aortic arch to the level of the bronchus. Its anterior limb extends 1 to 2 cm. anterior to and inferiorly along the course of the phrenic nerve to the inferior pulmonary ligament to join the posterior incision.

Flaps are elevated and retracted. The phrenic nerve is fully liberated throughout most of its upper mediastinal course so that it may be retracted anteriorly and posteriorly

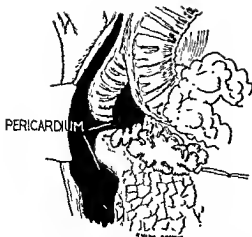


Fig. 22B-11. Right sides: subcarinal lymph nodes dissected onto lung from both bronchi and pericardium. Esophagus retracted posteriorly. (From W. G. Cohan, W. L. Watson, and J. L. Pool [7], courtesy *Journal of Thoracic Surgery*.)

thorough dissection of the retrocaval and peribronchial nodes.

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area along the intermediate bronchus can be obtained.

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Right Lower Lobe Radical Lobectomy

In a right lower lobe radical lobectomy (Figures 22B-9 and 22B-10), a procedure in which a middle lobe usually is included, dissection is

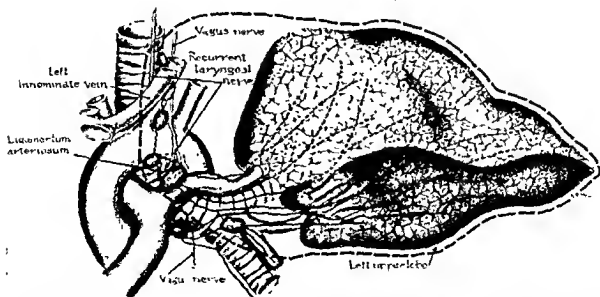


Fig. 22B-12. Left upper lobe radical lobectomy. Broken line marks limits of dissection. Note inclusion of inter-bronchial lymph node ("sump" position) between upper and lower lobe bronchi. Subcarinal nodes removed as a separate pocket. (From W. G. Cohan, courtesy *Journal of Thoracic Surgery*.)

the node of the ligamentum arteriosum* and that of the loop of the left recurrent nerve are freed. Lying between the superior border of the pulmonary artery and the anterior surface of the left main bronchus and extending beneath the aorta is a packet of nodes that must be dissected down toward the specimen. All these are included with the previously dissected mediastinal packet of tissue and tacked onto the lung surface.

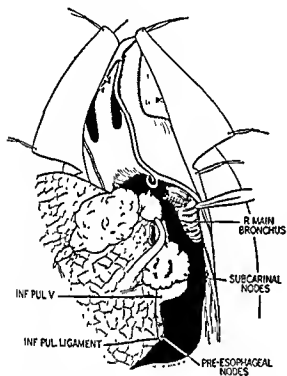


Fig 22B-16 Left upper lobe radical lobectomy The step illustrated shows dissection of nodes beneath the aorta and taken from a radical pneumonectomy drawing. Note divided ductus arteriosum (occasionally necessary).

The fissure between the upper and lower lobes is then divided and an approach made to the hilus. The incision made into the visceral pleura is curved anteriorly and posteriorly to meet the incision made previously in the mediastinal pleura. Starting with the bronchus to the left lower lobe (Figure 22B-12), the important lymph nodes that are readily available in the "sump" position are swept upward between the lower lobe bronchus and its corresponding artery up to

the take-off of the upper lobe bronchus. This last structure is isolated while dissecting the lymphatics toward the lung substance. By division of the artery to the left upper lobe, the dissection of nodes from the superior border of the left main stem bronchus is facilitated and all these are included with those from the subaortic and anterior mediastinal dissections. The subcarinal nodes are occasionally included as a separate packet. This practice becomes more routine in the light of the presence of metastases within them on several occasions.

Left Lower Lobe Radical Lobectomy

A left lower lobe radical lobectomy (Figure 22B-17) is similar to that on the right, including the pre-esophageal, subcarinal, and peribronchial nodes ("sump" position) (Figure 22B-18) located along the left main stem bronchus and immediately available around the left upper lobe bronchus. As on the right side, the left phrenic nerve is optionally crushed if a lower lobe is removed. The lingular portion of the left upper lobe is not included although, as has been noted, the right middle lobe is taken as part of a right lower lobe radical lobectomy.

Many patients who have a radical lobectomy performed are actual or potential pulmonary cripples, so that every effort is made to prevent compensatory emphysema of the lower lobes when an upper lobe lobectomy is performed. The space previously occupied by the upper lobes has been filled as follows: The parietal pleura occupying the dome and walls of the thorax is mobilized by extrapleural dissection so that it collapses on the superior surface of the lower lobe. An Ivalon sponge is then inserted in this extrapleural space, after it has been autoclaved in saline, tailored to size and shape, and rinsed in 200 to 300 cc. of a saline solution containing one million units of penicillin and 1 Gm. of streptomycin. Underwater drainage tubes are inserted separately, both into the pleural cavity and into this extrapleural space. The drainage of the pleural cavity is ended about the third or fourth day, and that of the extrapleural space about a day or two later. The extrapleural insertion of these Ivalon sponges has been performed in eight instances without any

* The ligamentum arteriosum has been divided in some instances to permit a more thorough node dissection beneath the arch of the aorta (Figure 22B-16).

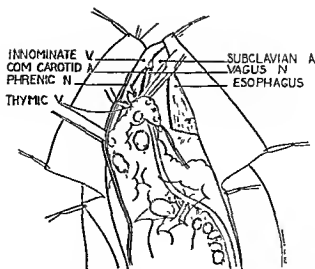


Fig. 22B-14. Left upper lobe radical lobectomy. Left side mediastinal lymph node dissection begun along left innominate vein. Phrenic nerve is retracted anteriorly.

by a Penrose drain as the dissection warrants (Figure 22B-14).

The apex of the anterior mediastinal dissection is at the undersurface of the left innominate vein at a point where it crosses the left subclavian artery. The areolar, node-bearing tissue is dissected off the vein, and several small branches must be separately identified and divided. The dissection proceeds anteriorly beneath the innominate vein as far as its entrance into the superior vena cava, dividing the highest intercostal and the thymic

branches along the way. This is the anterior limit of the dissection.

The posterior limit of the dissection is the subclavian artery (Figure 22B-15). The packet of tissue is swept down off the subclavian, common carotid, and innominate arteries and the aortic arch. The vagus nerve is carefully cleaned and, in particular, the large lymph node present in the space between the common carotid and subclavian arteries is included in the specimen.

Beneath the aortic arch (Figure 22B-16),

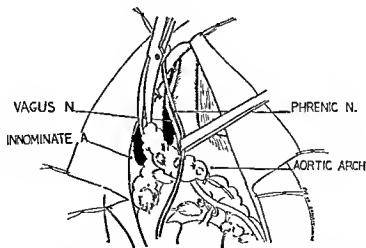


Fig. 22B-15. Left upper lobe radical lobectomy. Left side mediastinal dissection continued. Phrenic nerve retracted posteriorly and lymph node packet passed beneath it.

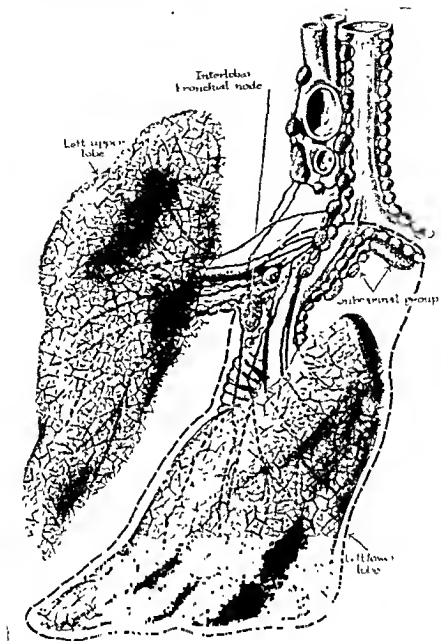


Fig 22B-18. Left lower lobe radical lobectomy; posterior view. (From W. G. Cohen, courtesy *Journal of Thoracic Surgery*.)

calcified tuberculous lymph nodes.

There are two major indications for a radical lobectomy, namely, for the treatment of (1) a primary cancer of the lung and (2) a lung tumor whose nature is ambiguous.

Indications for Radical Lobectomy for Primary Lung Cancer

Many variables influence the decision about the operation for primary cancer of the lung. These include age of the patient, position of the tumor, physiologic state of the patient be-

fore, during, and after the procedure, tumor size, position, and histology. It is therefore impossible to insist upon any one procedure as the sole method of surgical treatment and there are indications for operations of various complexities to meet varying conditions. These range from the wedge resection to the relatively complex, radical pneumonectomy that may also include portions of the trachea and the chest wall.

In these pulmonary resections, one is constantly striking a balance between removing

morbidity or mortality. The longest period that one has been in place is seven years (Figure 22B-19).

With the same principle in mind, there is the option of crushing the phrenic nerve by a clamp after the excision of the middle and lower lobes. This causes an elevation of the

INDICATIONS FOR RADICAL LOBECTOMY

In the following discussion it must be assumed that the pulmonary neoplasm is apparently contained within the confines of a lobe so that the transection of the lobar bronchus and vessels will provide a reasonable margin of uninvolved tissue. Such a determin-

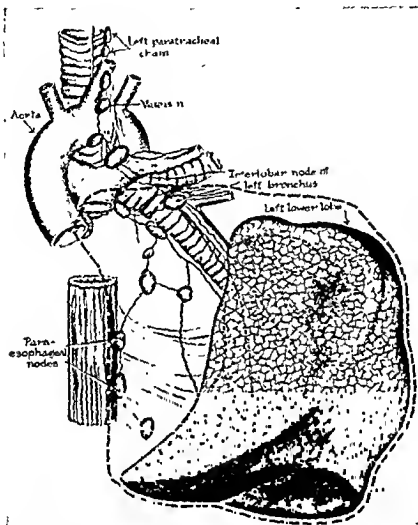


Fig 22B-17. Left lower lobe radical lobectomy; anterior view. Broken line indicates limits of dissection. Note inclusion of the interbronchial node ("hump" position) as well as the subcarinal paraesophageal groups. (From W. G. Cohen, courtesy *Journal of Thoracic Surgery*)

right leaf of the diaphragm, which will fill to a large extent the space left by the lobectomies. The virtue of this in preventing excessive compensatory emphysema of the right upper lobe as well as reducing dead space must be balanced against the paradoxical respirations and attendant mediastinal swing that will occur.

ation can, in part, be made preoperatively by bronchoscopic visualization of the major bronchi. At the time of thoracotomy, palpation and limited dissection about the hilus will also help to decide the feasibility of a lobectomy. At best this is only a gross estimate of tumor boundaries and can often be clouded by adjacent inflammation, fibrosis, and healed

ing, which is frequently held up to justify a lesser procedure for lung cancer, would not be tolerated in the treatment of cancer at other sites.

In addition to this objection to a block dissection of hilar and mediastinal lymph nodes as part of lung cancer surgery there are the following:

1. No statistical support up to now has shown a better cure rate for the more elaborate lymphatic dissection [14].

2. Long-term survivals have resulted from resection of lung tumors without this additional lymphatic dissection [9].

3. The probability of vascular invasion by the cancer is more significant in cure than lymph node involvement. Therefore, the excision of these lymphatics would not be of sufficient value in the control of the cancer [8].

4. The macroscopic examination of the mediastinal lymph nodes at the time of exploratory thoracotomy finds them either "obviously" negative or positive for the presence of metastases. If "negative," no further lymphatic dissection is deemed necessary, if "positive," additional lymphatic dissection is considered to be useless.

5. Microscopic analysis by frozen section is made of a "representative" mediastinal lymph node plucked at the time of exploration. If negative, the rest of the chain is presumed to be negative and allowed to remain intact, if positive, the prognosis is considered hopeless and a "palliative" excision of the lung tumor alone is completed.

6. The more anaplastic histologic types of lung cancer are so lethal that it is questionable whether surgery is indicated at all. If surgery is performed, only the simplest procedures are advocated and the more elaborate lymphatic dissection is considered to be futile.

As these arguments strike at the center of the controversy, their validity should be discussed.

1. Because long-term survivals have followed less elaborate procedures, there is an understandable hesitancy to add further surgical steps without first having concrete evidence of their value.

One of the most important supports for the more complex lymphatic dissection is that five-year survivors of lung cancer who had

hilar and mediastinal lymph node metastases removed by radical pneumonectomy are accumulating. The fact that long-term survivors exist in this category must be considered to be a tribute to the more extensive lymphatic dissection, for it is safe to say that these nodes would have been left behind in most instances had a simple pneumonectomy been performed. It should be remembered that such cancer-containing lymph nodes, if allowed to stay in place, would not have remained inert; the cancer contained within them would probably have behaved in a progressively lethal fashion. It could have grown, burst the nodal capsule, and invaded adjacent vital structures, and/or sent off metastases to adjacent lymphatics, eventually to enter the blood stream.

2. The success attributed to the cures effective by a limited procedure such as a simple lobectomy must be scrutinized in terms of the failures as well. In this regard, the work already quoted by Meade [15] and Thomas is strong evidence that cancer may be in the lymph nodes that lie beyond those removed by this operation as well as by a simple pneumonectomy.

In much the same fashion, although there are unquestionably cures that could be attributed to a simple mastectomy for breast cancer, many believe that danger attends an operation short of a radical mastectomy. For those who are interested in the surgical eradication of cancer, it is common knowledge that the first attempt at removal is the optimum time for cure. These limited procedures, which run the risk of being classified as "a small operation for a small cancer," leave too much to chance in the management of a disease as unpredictable and lethal as cancer.

3. In considering venous invasion as influencing judgment regarding the type of pulmonary resection to be undertaken, certain facts must be granted. Chief among these is that cancer of the lung all too frequently will metastasize to other organs by blood vascular routes, and it is not rare that this unfortunate fact becomes evident shortly after surgical excision. In an attempt to explain this, Johnson, Kirby, and Blakemore [14] found demonstrable blood invasion in 71 per cent of the surgical specimens (see Chap. 18). They concluded that with the finding of venous

cancer as thoroughly as possible and the physiologic ability of the patient to withstand such a removal, both during and following resection. Add to this the fact that there is a significant difference in the operative mortality between a lobectomy and a pneumonectomy, and it is understandable why opinions differ as to the procedure of choice.



Fig 228-19. Postoperative x-ray of patient in Figure 228-22 showing Ivalon sponge in right upper retropleural space and McKenzies clips in place along the paratracheal area. Note how little tracheal shift or diaphragmatic rise has occurred after a right upper and middle lobe radical lobectomy.

The simplest procedure and the one most easily supported by the patient and, at the same time, most sparing of respiratory tissue is a wedge or segmental resection. This, of course, can be used only for peripherally placed lung cancers. However limited this resection may be, five-year survivals have been reported following it, which suggests that in these instances, at least, the cancer of the lung had remained localized.

For the most part, however, this procedure is reserved for poor-risk patients, for most lung cancers are notoriously invasive and a wedge resection must be considered hazardous because of the possibility of cutting across malignant tumor tissue.

In the interest of providing a wider margin of normal tissue about these peripheral tumors, it seemed logical to utilize the natural boundaries of a lobe as the limits of excision.

The fact that each lobe had its own bronchovascular tributaries made a simple lobectomy feasible.

If these peripheral tumors can be encompassed by a simple lobectomy, the question naturally arises as to the need for a pneumonectomy, and this controversy is current at present [1, 9, 12]. The proponents of the lesser operation maintain that what is lost in the safety of the margin about the cancer is gained by a lower morbidity and mortality rate and better pulmonary function. Those who would advocate a pneumonectomy feel that it provides a more complete, intact unit about the cancer, that it is technically easier to perform, and that the morbidity and mortality rates, although presently high, can in time be considerably lowered.

To these controversial points has been added the question of the inclusion of hilar and mediastinal lymph nodes as part of the pulmonary resection. Some surgeons apparently resorted to plucking these out at random in the hope of obtaining prognostic and even curative reward. They felt that this was a working compromise, for the mediastinal lymphatics were considered to be "a morass" and, as such, impossible to excise completely.

In describing the step-by-step procedure of our version of a radical pneumonectomy in 1951 [7], it was our contention that there were definite anatomic landmarks which, although varying from right to left side, could be relied upon as arbitrary boundaries and that the lymphatics so obtained could be maintained as a block dissection with the lung. At no time was the claim made that all hilar and mediastinal lymphatics were completely encompassed by the line of resection, but some reassurance was gained from the fact that this problem was shared with operations for cancer elsewhere in the body. The fact that the lymphatics have to be transected at one point is no different for the mediastinal lymphatics from those of the breast as this organ is removed from the chest wall. It is true also for colon resection, radical neck dissections, and for cancer operations in general. In other words, there will always be the risk that the cancer will extend beyond the line of excision, or may have spread either by lymph or blood stream prior to surgery. This line of reason-

ing, which is frequently held up to justify a lesser procedure for lung cancer, would not be tolerated in the treatment of cancer at other sites

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invasion in specimens, the addition of lymph nodes may have little effect on outcome, although granting them possible prognostic significance.

Studies such as these add a great deal to the knowledge not only of the method of spread, but to prognosis as well. But it is difficult to understand how this should influence the inclusion of the hilar and mediastinal lymphatics. In the first place, vascular invasion by tumor, unless grossly evident at the time of exploratory thoracotomy, can be found only

Intrathoracic Tumors
node dissection or take out smaller portions of colon.

What is even more impressive is that microscopic evidence of vascular invasion does not always carry with it a bad prognosis. Even in Collier's series, there were four patients in this category who survived five years. In addition, Burford had three patients who showed blood vessel invasion and who lived five or more years, and two of whom had lymph node involvement as well. The author has four patients who have been alive five or more years

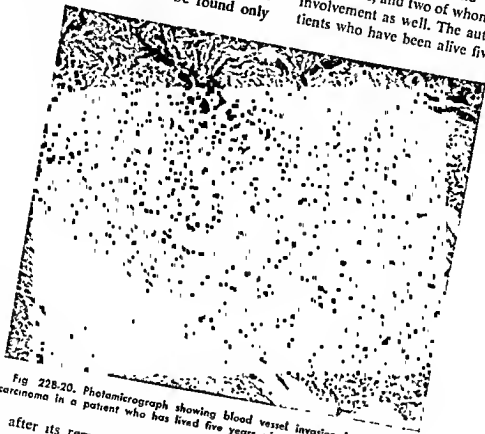


Fig 22B-20. Photomicrograph showing blood vessel invasion by epidermoid carcinoma in a patient who has lived five years after pulmonary surgery.

in the specimen after its removal. As such, this finding can not in any way influence selection of the procedure [7].

One of the best known analyses of lymph node metastases was done by Grinnell [13]. In his investigation, upon studying the primary cancers, he noted that in at least 35 per cent of the instances blood vessel invasion was microscopically found. He believed that this influenced prognosis, as did the finding of metastases in the regional lymphatics. However, it is doubtful indeed whether these findings would influence those who did colon resections, by making them do less of a lymph

who showed invasion of large pulmonary vessels by lung cancer (Figure 22B-20).

4. Observation and palpation of lymph nodes are very untrustworthy methods for the determination of the presence of metastases without them, and little reliance can be placed upon their size and consistency as aids in this regard. After all, exactly what size or what consistency guarantees the presence of contained metastases? It is true that enlarged lymph nodes at sites where these are not normally expected will naturally raise the question as to the nature of this enlargement, and this is so particularly if there is a cancer known to metastasize that could feed these

lymphatics. The cautious observer will be most reluctant to draw a conclusion from them. He will have experienced on more than one occasion the startling histologic report that these firm, enlarged nodes are indeed negative for metastases. On the other hand, he will also have been surprised that microscopic reports revealed the presence of metastases in lymph nodes that he had included in his dissection, although he thought they were "obviously" negative [16].

This equivocal nature of lymph nodes is most particularly applicable to those within the mediastinum, for these often have calcific deposits within them, making them harder than usual, or are enlarged in response to the inflammation that frequently surrounds a cancer of the lung. These misleading findings offer the most probable explanation for long-term survivals following a "palliative" lobectomy or pneumonectomy. These operations have usually been described as having been done to remove the primary lung cancer in the face of mediastinal lymph nodes that "obviously" contained metastases.

5. It is unreliable to base a lymphatic dissection upon the frozen section of a representative node plucked from the lymphatic group at the time of surgery. First, it would have to be a good representative node and as there are from twenty to fifty in the mediastinum, this would not be an easy choice. However, even if one grants that certain lymph nodes suggest themselves by their position in relation to the primary cancer as well as by their size and consistency as being more positive than others, it would be remembered first that it is technically difficult to do a frozen section on a lymph node; secondly, that lymph nodes can have small deposits at one edge that may fail to be part of the section viewed and can be revealed only by serial sections [19]. A third objection, although of infrequent occurrence, is that oat-cell carcinoma deposited in lymph nodes is almost indistinguishable from hyperplastic lymphoid tissue, particularly at the time of frozen section. One other point of reasoning would seem to be weak. If the node selected is negative for cancer, why must it be assumed that all the others in the group are innocent as well? If it is positive, does this mean that all the others in its group are

to be so incriminated, and as such impossible to encompass by resection, and indicative of a hopeless setting? (Figure 22B-21.)

6. In the more anaplastic types of cancer, including the oat-cell variety, the prognosis is undoubtedly poor. There is real question indeed as to whether a patient should be sub-



Fig 22B-21. Photomicrograph showing a small focus of metastatic epidermoid carcinoma from the lung in one paratracheal lymph node out of eight that were sectioned.

jected to a surgical procedure for tumors as notorious for their tendency to rapid spread beyond the thorax. This finds support in the fact noted by Collier, Blakemore, Kyle, Enterline, Kirby, and Johnson that all anaplastic types of cancer showed invasion of blood vessels in their specimens. It is rare to have a patient with oat-cell carcinoma of the lung who has lived more than twelve months following its diagnosis.

Most of these anaplastic cancers are radio-sensitive, and one might properly ask if irradiation is not indeed the modality of choice. However, in the midst of the pessimism that understandably surrounds these tumors, it should be noted that some patients do survive five or more years after removal.

In support of this, Burford [4] states: "The high incidence of five-year survival we obtained in cases of undifferentiated carcinoma, and in cases with gross lymph node and blood vessel invasion, has reinforced our feeling that the most important step in curing cancer is still the surgical removal of all tumor-containing tissue, and that all patients should be considered for resection if there is reasonable belief that this can be done." If any surgical procedure is performed, it should certainly take into consideration the hilar and mediastinal lymphatic dissection because, in addition to their strong tendency to vascular invasion, they involve lymph nodes as well. In other words, if resection is indicated at all, it might as well provide every chance for survival.

In summary and in the light of the above considerations, it would seem that with so much doubt as to the significance of the contents of the hilar and mediastinal lymph nodes at the time of surgery, it is far better practice to remove these by means of a logically constructed, reasonably well-defined anatomic dissection. It is our conviction that a radical pneumonectomy, as described in our clinic, fulfills these, and we believe it to be the treatment of choice for a primary cancer of the lung, when it is permitted. In most instances where there would be a contraindication to the removal of the entire lung, a radical lobectomy has been instituted as a compromise procedure.

Indications for Radical Lobectomy for a Lung Tumor Whose Nature Is Ambiguous

There are two clinical settings in which ambiguity surrounds the nature of a lung tumor: (1) A cancer primary at another site is associated with a solitary lung shadow. This lung shadow may represent either a separate primary lung cancer or a solitary metastasis. (2) A mass in the lung resembles cancer, but the diagnosis cannot be established with absolute finality, either before or during the operation.

1. In our experience, we have been impressed with the frequency with which multiple cancers, one of which is primary in the lung, have coexisted. We have amassed 165 such instances. In the same period (1926-

1958), there have been forty-six solitary metastases removed. It is not safe, therefore, to presume that a solitary lung shadow, either synchronous or metachronous with a cancer elsewhere in the body, is a metastasis. In fact, these figures suggest that it might be four to one in favor of its being a separate primary cancer. In either event, whether separate pri-

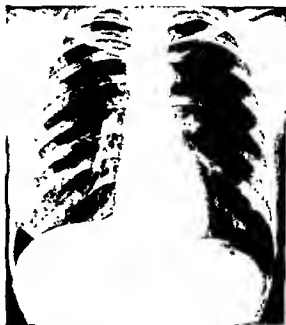


Fig. 22B-22. X-ray showing metastatic teratocarcinoma of ovary in right upper lobe which had a daughter metastasis in the azygos vein node (same patient as Figure 22B-19). Patient had right upper and middle lobe radical lobectomy. Patient is without evidence of cancer eight years later.

mary cancer or metastasis, we know that local lymphatic extension can occur. This does not need documentation in the case of primary cancer of the lung, but in nine metastases to the lung removed by radical lobectomy, there were six instances in which daughter metastases existed in the hilar and mediastinal lymphatics (Table 22B-4). In other words, a metastasis from another site deposited within the lung parenchyma can behave as though it had its origin there and its metastases can in turn proceed by lymphatic or venous routes (Figure 22B-22).

2. As is often the case, an area of inflammation will frequently be present in association with cancer of the lung. This condition usually follows an obstruction of one of the bronchioles, which can produce distal atelectasis, pneumonia, and abscesses. It is not al-

ways possible, by preoperative cytologic studies or by biopsy at the time of thoracotomy, to obtain a diagnosis either of a benign or a malignant process. In other words, it is not infrequent at the time of exploratory thoracotomy that repeated biopsies and frozen section analyses of suspicious lung regions can be reported as showing chronic inflammation. This leaves in doubt whether these sections are truly representative, or whether there is a more cryptically placed cancer. In this equivocal setting it is probably wisest to assume cancer to be present. As a compromise, therefore, a radical lobectomy is performed. This operation, while fulfilling the desirability of removing the tumefaction in the lung and many of its regional lymphatics, does not subject the patient to the increased hazard of a pneumonectomy.

END RESULTS OF RADICAL LOBECTOMY

Forty-eight radical lobectomies were performed in the seven-year period from March,

TABLE 22B-1.—RADICAL LOBECTOMY FOR CANCER AND ALLIED DISEASES (Author's Series)

Number performed, March, 1951–March, 1958	48
Primary lung cancer	34
Metastases to lung	9
Inflammatory diseases	5
Postoperative deaths	5

TABLE 22B-2.—RADICAL LOBECTOMY FOR CANCER: FREQUENCY OF METASTASIS TO REGIONAL LYMPH NODES

Patients who had either primary lung cancer or a metastasis to lung removed	43
Specimens showing metastatic deposits in mediastinal nodes beyond those usually taken by simple lobectomy	17
Per cent positive (2 not stated)	17/41 (42 per cent)
Conditions	
Primary lung cancer	11
Metastases to lung	6

1951, to March, 1958 (Table 22B-1) There were no postoperative complications other than those that caused five postoperative

deaths from gastrointestinal hemorrhage, overwhelming infection, myocardial infarct, hemorrhage in the operating room with cardiac failure, and one death of undetermined origin. This last occurred in a woman who had a right middle and upper lobe radical lobectomy in July, 1954, for an adenocarcinoma of the lung, and the last operation was a left upper lobe lobectomy in December, 1955, for terminal bronchiolar carcinoma.

This mortality rate is high. There is no reason, however, to attribute any of the deaths to the more elaborate lymphatic dissection, a contention that is supported by the fact that there have been no postoperative complications or mortality in the last thirteen patients undergoing radical lobectomy. Over half of these operations were performed by the surgical Residents under supervision as one of their earliest thoracic procedures.

End Results of Radical Lobectomy for Primary Lung Cancer

There were thirty-four primary lung cancers removed by this method. The histologic types, as may be seen in Table 22B-3, in-

TABLE 22B-3.—RADICAL LOBECTOMY FOR CANCER: RELATION OF HISTOLOGIC TYPE OF PRIMARY LUNG CANCER TO NODAL METASTASES

Extrapulmonic nodes containing metastatic cancer	
Epidermoid carcinoma	3
Terminal bronchiolar carcinoma	4
Anaplastic carcinoma	1
Adenosquamous carcinoma	1
Adenocarcinoma	2
Total	11
Extrapulmonic nodes free of metastatic cancer	
Epidermoid carcinoma	7
Terminal bronchiolar carcinoma	5
Adenocarcinoma	4
Mucoepidermoid carcinoma	3
Anaplastic carcinoma	1
Pleomorphic reticulum-cell sarcoma	1
Total	21
Not mentioned	2

cluded the prevalent varieties except oat-cell carcinoma. In this group of thirty-four, eleven patients had lymph nodes containing cancer beyond the limits of a simple lobectomy.

These again included five different histologic types.

There were four patients with primary lung cancer operated on five or more years ago (Table 22B-4). Of these, one patient with pri-

nces to the lung were operated on five or more years ago (Table 22B-4), and three of them had positively involved mediastinal lymph nodes. These included metastases from rectal cancer, a teratocarcinoma of the ovary, and an osteogenic sarcoma. The first three patients are alive and well, and the last-named died of cancer seven years after radical lobectomy.

TABLE 22B-4.—RADICAL LOBECTOMY FOR CANCER. DEFINITIVE END RESULTS

Patients operated on 5 or more years ago	8
Primary lung cancer	4
Metastases to lung	4
Patients with metastatic cancer in mediastinal nodes	5
Alive and well 5 or more years	3
Tumor diagnosis of the survivors with mediastinal nodes containing metastatic cancer	
Primary adenosquamous carcinoma of lung	1
Metastatic rectal carcinoma	1
Metastatic teratocarcinoma of ovary	1
Osteogenic sarcoma (died of recurrence 7 years after radical lobectomy)	1
Patients with mediastinal nodes free of cancer	2
Died postoperatively	1
No evidence cancer	1

mary adenosquamous carcinoma of the right upper lobe has lived over five years, although having had extrapulmonic lymph node metastases. One patient with negative extrapulmonic lymph nodes is alive and well. One patient died postoperatively of myocardial infarct, and one died of recurrent cancer thirteen months later.

End Results of Radical Lobectomy for Cancer Metastatic to the Lung

Of the forty-eight radical lobectomies, nine were performed for metastases to the lung (Table 22B-1). There was no postoperative morbidity or mortality. The types of primary cancers included: two breast cancers, one instance each of rectal cancer, renal cancer, melanoma, osteogenic sarcoma, rhabdomyosarcoma, teratocarcinoma of the ovary, fibrosarcoma.

Of these nine patients, six had hilar and mediastinal lymph nodes containing cancer beyond the limits of excision of a simple lobectomy.

Four patients in the group having metas-

MULTIPLE PRIMARY CANCERS

There were six instances of double primary cancers, in which one of each pair was in the lung. Other sites included: tongue, two; breast, two; larynx, one; lung, one.

Radical Lobectomy for Nonneoplastic Lung Disease

There were five radical lobectomies performed for tumorlike lung conditions that subsequently proved to be inflammatory. These included: four chronic pneumonias with atelectasis and/or abscess, and one lipid pneumonia. There were no complications or mortalities in this series.

DISCUSSION

In reviewing the results previously listed, it can be seen in Table 22B-2 that of forty-one patients operated on either for primary cancer or metastatic cancer to lung by means of a radical lobectomy, seventeen (or about 42 per cent) had metastatic involvement of hilar and/or mediastinal lymph nodes. In other words, 42 per cent had more cancer removed by a radical lobectomy than would have been removed had a simple lobectomy been performed.

Of these seventeen patients, five were operated on five or more years ago, and three are alive without evidence of cancer at this time.

The use of a radical lobectomy for the excision of primary lung cancer in this series was for the most part in poor-risk individuals who had moderately severe cardiac disorders, bronchial asthma, emphysema, and/or advanced years. In addition, in the five instances mentioned above, there was the association with another primary cancer at another site.

It is not within the province of this chapter to argue the value of a lobectomy versus a pneumonectomy for the treatment of peripherally placed primary lung cancer. However,

if the more limited procedure is performed, it is felt that the addition of the more extensive lymph node dissection improves the probabilities of cure. There is even suggestive evidence, we tentatively feel, that for cancers in the right upper lobe, a right upper lobe radical lobectomy, including the nodes in the "sump" position, might become the treatment of choice. Although such a confining procedure risks the possibility that retrograde lymphatic spread would extend the cancer beyond its arbitrary limits of dissection, nevertheless the sum total of survival that takes into consideration operative mortality rates must be considered. However, these rates are not static and, it is hoped, can be improved to a reasonable level.

Such a limited procedure as is described would be theoretically less advantageous for primary lung cancers in the right middle and right lower lobes, for the usual lymphatic currents would tend to favor metastases at locations superior to and beyond the usual limits of excision of a right middle and lower lobe radical lobectomy. The same is true for primary cancers in the left lower lobe. Here the possibility of metastases extending first to the subcarinal and/or right paratracheal nodes makes a more complete extirpation more difficult. Neoplasms in the left upper lobe (particularly the superior portion) are perhaps theoretically more favorable than those in the left lower lobe because their lymph node

metastases might remain ipsilateral. However, they too have a tendency to extend to the right side by way of the subcarinal and anterior mediastinal channels.

Just what extra chance for survival is afforded by the inclusion of the lymph nodes as part of a radical lobectomy or radical pneumonectomy is difficult to determine at present because of the limited number of procedures performed. The same is true in defining prognosis derived from the pathologic material alone.

Although a tentative attitude is necessary at this time, one fact seems to be evident: each case is a law unto itself, and survival probably is the result of the interplay of various pathologic states with the intangible forces of host resistance. It is therefore unwise to permit a single, isolated clinical or pathologic feature (for example, the threat of blood vessel invasion or the finding of a single mediastinal lymph node positive for cancer) so to dominate the picture that all aggression ceases. Instead, it would seem wiser to advocate an operation that attempts to eradicate most of the tangible elements in lung cancer, thus leaving less to chance. To our mind, a radical pneumonectomy and a radical lobectomy best fulfill this purpose.

Grateful acknowledgment is made to Mrs. Phyllis Pearce Atkinson for her many suggestions and help in compiling this chapter.

These again included five different histologic types.

There were four patients with primary lung cancer operated on five or more years ago (Table 22B-4). Of these, one patient with pri-

tases to the lung were operated on five or more years ago (Table 22B-4), and three of them had positively involved mediastinal lymph nodes. These included metastases from rectal cancer, a teratocarcinoma of the ovary, and an osteogenic sarcoma. The first three patients are alive and well, and the last-named died of cancer seven years after radical lobectomy.

TABLE 22B-4.—RADICAL LOBECTOMY FOR CANCER: DEFINITIVE END RESULTS

Patients operated on 5 or more years ago	8
Primary lung cancer	4
Metastases to lung	4
Patients with metastatic cancer in mediastinal nodes	5
Alive and well 5 or more years	3
Tumor diagnosis of the survivors with mediastinal nodes containing metastatic cancer	
Primary adenosquamous carcinoma of lung	1
Metastatic rectal carcinoma	1
Metastatic teratocarcinoma of ovary	1
Osteogenic sarcoma (died of recurrence 7 years after radical lobectomy)	1
Patients with mediastinal nodes free of cancer	2
Died postoperatively	1
No evidence cancer	1

mary adenosquamous carcinoma of the right upper lobe has lived over five years, although having had extrapulmonic lymph node metastases. One patient with negative extrapulmonic lymph nodes is alive and well. One patient died postoperatively of myocardial infarct, and one died of recurrent cancer thirteen months later.

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CONTRAINDICATIONS TO RADICAL EXCISION OF CONTIGUOUS STRUCTURES

The presence of blood-stained fluid containing malignant cells or of paralysis of the vocal cord, in our opinion, constitutes a contraindication not only to resection of a portion of the thoracic cage but to exploratory thoracotomy as well.

If the necessity for the removal of contiguous structures is anticipated preoperatively, it is advisable to obtain lymph nodes from the fat pad over the anterior scalenus muscle through a cervical incision before exploring the thorax. If the lymph nodes are involved with carcinoma, exploration should be abandoned.

The proved presence of distant metastasis will preclude the advisability of resections of the chest wall or the structures of the thorax in connection with pulmonary resection. The only possible exception to this rule will be in cases with intractable pain that appears to result from chest wall invasion.

IMPORTANCE OF THE ANATOMIC POSITION OF LUNG CANCER INVADING CONTIGUOUS STRUCTURES

Resections of large portions of the chest wall are easier in the lower chest and more difficult near the apex. Invasion of the sternum does not present an insurmountable technical problem, but careful inspection of the mediastinum will often reveal extensions of the neoplasm that cannot be resected.

It is of particular importance, if contiguous structures are to be excised, that the pneumonectomy be of the type described by P. R. Allison [1]. The pulmonary vein should be divided within the pericardium and the tissues removed in continuity, including the pericardium and mediastinal pleura. (See Chap. 19 for the technic of mediastinal resection.)

Cancers of the lung situated in the posterior superior sulcus (Pancoast tumor) should not be resected if they have invaded the brachial plexus, sympathetic nervous system, or the blood supply to the upper extremities. These neoplasms vary in malignant potentialities but are frequently well differentiated. Usually it is impossible to obtain a positive tissue diag-

nosis by bronchoscopy. The Papanicolaou technic may hint of the diagnosis, and roentgen evidence for practical purposes may establish it. (See also Chap. 28.)

It is apparent that resection of contiguous structures would call for a sacrifice of the upper extremity with little hope of a long-term arrest. Exploratory thoracotomy however, is mandatory. In a few cases the lesion will be a primary nerve tumor (one in many hundreds, in our experience) but a tissue diagnosis can be made. Division of the second, third, fourth, and fifth intercostal nerves and the intercostal humeral nerve will usually result in gratifying relief of pain. Many of these patients will live for several years and be able to carry on a productive life. It is of interest that a posterosuperior sulcus tumor may produce symptoms that are those of cervical disc disease. Two known cases of futile therapy for cervical discs have been brought to our attention in patients with cancer of the lung.

Invasion of the chest wall near the body of the vertebra is more an academic question than a practical one. This is rarely seen except in cases with pleural involvement and obvious inoperable situations. Involvement of major mediastinal structures usually indicates total inoperability. Removal of the parietal pleura in cases with massive pleural involvement, along with portions of the diaphragm if necessary, has been advocated by Cotton. It is doubtful that this extremely radical approach is worth while.

FACTORS DETERMINING THE FEASIBILITY OF RESECTION OF CONTIGUOUS STRUCTURES INVOLVED BY BRONCHOGENIC CARCINOMA

The feasibility of resecting and the decision to resect portions of the chest wall or other structures involved by lung cancer are not settled in the conference room. Only exposure of the neoplasm and knowledge of the cell type and its anatomic position will permit a rational evaluation. Timidity is perhaps worse than ignorance.

The surgeon must determine to the best of his ability, first, whether the patient will survive the operation; second, if there is a reasonable chance of palliation and a remote chance

Resection of Pulmonary Neoplasms That Have Extended to Contiguous Organs

*Brian B. Blades
and
R. Carl Garby*

The necessity for the resection of pulmonary neoplasms that have extended to contiguous structures can only result from late neglected cases or from invasion of the thoracic cage by a silent peripheral carcinoma. There are no reliable data concerning the results of resections of pulmonary neoplasms and involved contiguous structures. It is safe to predict, however, that few cases will be arrested for a long period since a neoplasm that has extended beyond the boundaries of lung tissue indicates far-advanced cancer.

The decision to perform radical excision of contiguous structures involved by lung cancer will, therefore, first be judged on a basis of palliative benefits, with the remote chance of long-term or temporary arrest.

TYPE OF CARCINOMA SUITED FOR RADICAL RESECTION

There is considerable controversy concerning the ultimate prognosis of carcinoma of the lung, depending on histologic features. Neuhof and Aufses [6] have stated that "The microscopic features of carcinoma of the lung bear no significant relationship to ultimate prognosis." This may be true for cancers that are confined within lung tissues, but it cannot be applied if extirpation of any part of the thoracic wall or other contiguous tissues is undertaken, either with a hope of cure or for palliation.

If contiguous structures are involved, Adams' estimate of the importance of cell type should be accepted. He believes "The cell

type of carcinoma found by microscopic examinations is the most important single consideration in the estimation of prognosis after resection. If the growth is undifferentiated or oat cell in type, less than a year of life may be expected" [2]. Radical resections of contiguous structures invaded by highly undifferentiated carcinoma are, therefore, undesirable. Conversely, this technic should be employed without hesitation in the presence of well-differentiated squamous-cell carcinomas.

In this connection, it is appropriate to record a word of warning concerning the evaluation of radical excisional surgery with removal of other tissues than the lung in cases with highly differentiated squamous-cell carcinoma. The neoplasms may be indolent and not progress for many years. At the George Washington University Hospital we have a proved case of squamous-cell cancer of the lung that had been present for seven years and was finally treated by pneumonectomy when the patient developed hemoptysis. Surgical intervention had been recommended but refused by the patient until severe hemorrhage occurred. The lung could be resected even after the carcinoma had been present for a long time.

The early work of Tuttle and Womack [10] suggests that peripheral bronchogenic carcinomas are more apt to be highly malignant and undifferentiated than those arising in the larger bronchi. Invasion of the thoracic cage wall, of course, be more common for such peripheral tumors.

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The surgeon must determine to the best of his ability, first, whether the patient will survive the operation; second, if there is a reasonable chance of palliation and a remote chance

of cure, and third, whether he will be able to close the wound.

Wound Closure Following Resection of the Chest Wall

Wide excision of cancer tissue offers the one chance of cure but there are certain anatomic limitations that dictate the extent of the resection. New technics in blood vessel grafts suggest that even the great vessels might be resected. Large segments of the chest wall can be resected with little danger.

Most defects of the thoracic cage can be repaired by plastic procedures involving only the muscles, periosteum, and adjacent ribs. If the defects are so large that the tissue at hand is not adequate, fascia lata may be employed; and recently our experiences indicate that steel mesh gauze will be useful in reconstruction of the thoracic cage (Figure 23-1). Large chest wall defects are often necessary in connection with excisions of chest wall tumors of various types. (See Chap. 33 for a description of wound closure after resecting portions of the chest wall.)

The fundamental problem, however, is not concerned with restoration of the chest wall or contiguous-structure continuity, but with the feasibility and advisability of radical extirpation of cancer that has transgressed the boundaries of the organ in which it originated.



Fig 23-1. Roentgenogram showing a large stainless steel mesh prosthesis, which was necessary after excision of a large portion of a chest wall that had been involved with carcinoma.

Available surgical technics outlined by various thoracic surgeons erase the fear of being unable to restore the continuity of the thoracic cage. The indefinable quality known as surgical judgment must temporarily determine whether or not contiguous structures involved by cancer should be resected.

Surgical Treatment of Metastases to the Lung

Hirom T. Langston

To remove a secondary cancerous focus lying outside the anatomic field of the primary tumor from which it sprang is to be bold. The possibility, however, that the metastasis in question can be the only remaining bit of the cancer, as is substantiated by recorded successes when coupled with the relative safety of well-ordered pulmonary resection, justifies such aggressive action insofar as secondary pulmonary deposits are concerned. Obviously, these stipulations exclude from consideration patients with uncontrolled primary tumors and those with evidence of widespread cancerous dissemination.

Accepting the ideal situation (which would be typified by a chest roentgenogram presenting a well-circumscribed mass in one pulmonary lobe), not only are we spurred on to aggressiveness by its solitary appearance, but our hand is further reinforced by the possibility that this pulmonary lesion might be a second primary cancer or other lesion for which extirpation is mandatory or advisable (see p. 406).

NATURE OF PULMONARY METASTASES

The lungs are a predilect site for the development of metastases, and virtually any malignant tumor can be responsible for secondary deposits therein. It has been estimated that only some 20 per cent of living individuals presenting evidence of pulmonary metastases have them so disposed anatomically that surgical resection might be feasible. However, if from this group are excluded as unsuited those patients with uncontrolled primary tumors or evidence of extrapulmonary metastasis as well, the figure falls to around 10 per cent. Actually, the final rate of acceptance for

surgical extirpation in one such group was less than 1 per cent [9].

The hypernephroma has perhaps been accorded highest popularity as a source of solitary or "cannon ball" metastasis; but when one reviews the cases that have sufficiently well satisfied the necessary clinical criteria of selection actually to be subjected to resections for pulmonary metastasis, carcinomas of the large bowel are the most frequent, followed by hypernephromas and sarcomas of the soft tissues, the fibrosarcomas accounting for the greatest number of the latter [10].

As with many of the other considerations concerning neoplastic diseases, the details governing the appearance and development of lung metastases are far from clear. It does seem generally accepted, however, that they arise in tumor emboli that are filtered out of the blood stream by the vascular mesh of the pulmonary circulation [13].

It seems probable that such tumor emboli may be more numerous and more frequent than is comforting to contemplate. Why only a few or, more particularly, why a single cluster only of neoplastic cells should flourish and others wither is intriguing indeed.

Typically, lung metastases of solitary character develop within the parenchyma, but they may lodge in such fashion as to invade and obstruct the bronchus in a manner reminiscent of a primary bronchogenic cancer. Bronchial involvement by lung metastasis, as demonstrated at post-mortem examination, occurred in some 18 per cent of patients in one series [8], but this incidence may have to be revised to between 35 per cent and 40 per cent [10] on the basis of more discriminating and detailed clinical reviews.

It is thus apparent that, whereas lung involvement is frequent in the late stages of cancer, the occurrence of a solitary metastasis (or closely grouped metastases) amenable to surgical extirpation as the only remaining bit or bits of the cancer is relatively uncommon. The growing interest in this possibility, however, may rapidly swell the list of successful results and provide the statistical data necessary for more accurate estimations of incidence.

CLINICAL FEATURES OF NEOPLASMS METASTATIC TO THE LUNG

An unabridged discussion of the subject at hand would lead to tedious consideration of the many potential combinations that a metastatic cancer could have with respect to the primary tumor, the interrelation of multiple metastatic deposits, and the complexities of symptomatology engendered by the possible anatomic sites of the lesion or lesions. A few broad premises can, however, be called upon to abridge the topic.

Recognition of the Pulmonary Metastasis

The presence of a lung metastasis is usually demonstrated by a roentgenogram. This may be obtained because of the presence of symptoms, or as part of a routine check-up examination.

SYMPTOMATOLOGY

The symptoms produced by a lung metastasis are dependent primarily upon the location of the growth. Tumors situated in the parenchyma of the lung and, therefore, away from a major bronchial radical may be and usually are entirely asymptomatic. Symptoms can easily be produced by them, however, if they extend to the pleura or undergo cavitation.

Extension through the visceral pleura into a free pleural space usually results in a pleural effusion that is typically although not necessarily bloody. Such an occurrence can be responsible for the production of cough and dyspnea. If the extension occurs across an obliterated pleural space, invasion of the parietes may result in pain of pleuritic character, if not the more intractable pain of direct

involvement of the intercostal nerve or nerves themselves.

If cavitation occurs, conceivably as a result of the mass outstripping its blood supply as it grows, productive cough and hemoptysis can be expected to supervene, and if the communication with the bronchus leads to secondary infection of the cavity, a clinical picture suggesting a lung abscess may be produced. Interestingly enough, actual tissue may occasionally be coughed up by such patients [9] and can be sufficiently well preserved to permit accurate histopathologic classification.

If, on the other hand, the neoplasm so disposes itself as to encroach upon a major subdivision of the bronchial tree, the symptoms produced by it are primarily those of bronchial disease and consist basically of cough and/or hemoptysis accompanying the signs of bronchial obstruction, which in turn may range from merely a wheeze to the more complex symptomatology attendant upon lobar or pulmonary atelectasis with or without superimposed suppurative.

ROENTGENOGRAPHY

Roentgenographically the peripheral neoplasm is recognized as a mass within the lung field or is signaled by the changes produced by its concomitant effusion. Invasion of the chest wall may be difficult to recognize unless erosion of an overlying rib is demonstrable. The centrally placed tumor, involving the bronchogram, its presence being heralded by evidence of bronchial obstruction: atelectasis or obstruction emphysema.

Relation of the Metastasis to Its Primary Tumor

For the sake of completeness, we must consider three possible combinations: the metastatic, the synchronous, and the precocious

PRECOCIOUS METASTASIS

This category takes in those rare situations where all attention is focused upon the pulmonary lesion, the primary tumor being silent (Figure 24-1). The diagnosis of such an occurrence usually depends upon a careful histologic study of the lung tumor itself, leading

Intrathoracic Tumors

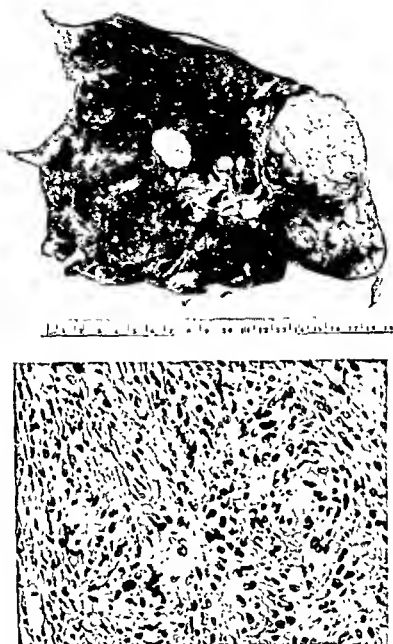


Fig 24-1. Illustrating some of the features of the precocious metastasis as well as the vagaries of pulmonary tumors, be they primary or secondary (Top) Gross specimen. Two circumscribed neoplasms that were seen by chest roentgenogram in a fifty-seven-year-old female who had no pulmonary symptoms. No evidence of another neoplasm existed. (Bottom) The lung was resected and revealed a metastatic fibrosarcoma. The primary site is unknown, unless it was the uterus removed twelve years before for "fibroids"

to proof that it is not primary in the lung. Should perchance the tumor be accessible for biopsy at bronchoscopy, the correct diagnosis may possibly be made by this means. In the more common peripheral location, however, thoracotomy will be required to provide tissue for histologic study. Resorting to frozen-section examination at the time of thoracotomy

may not permit differentiation of a metastatic from a primary tumor inasmuch as such a differential diagnosis calls for very clearly defined histologic features often not attainable by such quick methods. In any event, once the diagnosis is established, there must needs be an often frustrating search for the undiscovered primary tumor, and this usually after the



Fig. 24.2 (Top) These two roentgenograms illustrate the more or less typical findings in solitary (presumably) metachronous metastasis to the lung in a forty-two-year-old female who had a resection of the low sigmoid colon for carcinoma one year previously. The solitary pulmonary metastasis was discovered by routine roentgenography. There were no pulmonary symptoms. (Bottom) This tumor, histologically typical of a pulmonary metastasis from a colonic carcinoma, was resected by pulmonary lobectomy.

metastatic cancer has been accorded the resectional treatment demanded for a primary lung cancer with which it was confused.

Since this relation between a primary tumor and its metastasis does not fall within the actual scope of this chapter, it can be dismissed without further consideration.

METACHRONOUS METASTASIS: THE SYNCHRONOUS METASTASIS

The appearance of a metachronous (Figure 24-2) or a synchronous (Figure 24-3) pulmonary metastasis, however, calls for further elaboration. Whether its presence is suggested by the appearance of symptoms or is heralded



Fig. 243 Presents the problem of the synchronous metastasis noted in a fifty-nine-year-old male. (Top) Rectal symptoms led to the diagnosis of a rectal carcinoma (Bottom) The pulmonary tumor was found by routine roentgenography. Because of signs and symptoms of pulmonary osteoarthritis, it is speculated that the lung tumor is a second primary tumor.

by roentgenographically demonstrated pathology, the answer to certain definite questions must be sought.

Is the lesion seen on the roentgenogram or evidenced by pulmonary symptoms a metastasis? Is it an inflammatory lesion and therefore unrelated to neoplasia? Or, finally, could it be a second primary cancer? Obviously, in the face of a history of an eradicated primary cancer (metachronous lesion) or a known but

as yet untreated cancer elsewhere in the body (synchronous lesion), the first and most logi-

* EDITORIAL NOTE Before performing a thoracotomy for a presumptive solitary metastasis in the lung, it is considered good policy to study the lung fields more critically by the aid of sagittal and anteroposterior tomography. This procedure on numerous occasions has demonstrated that in addition to the discrete metastatic focus visible on the conventional roentgenogram, other smaller, disseminated, and even bilateral metastases become apparent, a circumstance that has enabled both the surgeon and the patient to escape a futile operation.

cal assumption is that the pulmonary lesion is a metastasis.

Diagnostic Procedures

The diagnostic exercises required to demonstrate the lesion's neoplastic or nonneoplastic nature are highly germane to this discussion, but certain of the procedures do require comment.

BRONCHOSCOPY

Bronchoscopy is most valuable in the event of bronchial symptoms. A biopsy obtained by this means will be valuable indeed.

CYTOLOGY OF BRONCHIAL SECRETION

Exfoliation of cancer cells from a metastasis seems to be a relatively rare phenomenon and the percentage accuracy of cytologic diagnosis is proportionately low (10 to 12 per cent) [4]. The explanation for this paucity of positive cytologic findings in pulmonary metastases apparently lies in the fact that the bronchial mucosa can and does remain intact over the site of a metastatic tumor growing into the bronchial wall, in contrast to a bronchogenic carcinoma, which implicates the mucosa originally and therefore is not barred from free exfoliation along its surface.

ASPIRATION BIOPSY

This diagnostic maneuver is mentioned principally for condemnation.

INSUFFLATION OF AIR

Pneumothorax may at times be useful in clarifying the anatomic location of certain lesions that may impinge upon the boundaries of the hemithorax, presupposing, of course, that a free pleural space exists.

MISCELLANEOUS CONSIDERATIONS

Various tests for sensitivity to such infections as tuberculosis, coccidioidomycosis, and histoplasmosis, etc., are mentioned for completeness.

Even differentiation between a metastasis and a second primary neoplasm, be it synchronous or metachronous, demands great diagnostic acumen, because the pathologist must rely on his ability to recognize the parent

cell responsible for the mitotic descendants in question (Figures 24-4 and 24-5).

MANAGEMENT OF A PULMONARY LESION BELIEVED TO BE A CANCER METASTASIS

Indications for Surgical Exploration and Resection

There must be some reasonable assurance that the pulmonary lesion might be the one remaining portion of the neoplasm, or that it is a lesion unrelated to the known cancer, before exploration of the thorax with the intent of resecting it is justified.

CRITERIA OF MANAGEMENT IN METACHRONOUS LESIONS

In metachronous lesions, careful appraisal of the adequacy with which the former cancer has been treated is paramount. When it occurred in accessible regions of the body, direct examination, including biopsy of any suspicious areas, is justified. In visceral cancer this appraisal usually is done by much more indirect methods, but should be undertaken with all diligence. If all clinical findings are negative for evidence of local recurrence, it seems hardly justifiable in remote regions of the body to resort to preliminary exploratory operations, it being rather more logical to care for the known pulmonary tumor first. Thus, if the situation in question gives no evidence of local recurrence or generalized dissemination of the original neoplasm, attention can be focused upon the pulmonary lesion.

In Peripheral Location

In the event that the lung lesion appears as a discrete intrapulmonary mass, relatively little time need be consumed in diagnostic study because the great probability is that it represents a neoplasm and even should it be of other etiology, its eradication is probably justifiable.

Multiplicity of pulmonary lesions, even though they be confined to one lung or, preferably, one lobe of the lung, indicates caution but probably should still be considered for exploration and resection. The possibility that other small and therefore unrecognizable lesions may be present in addition cannot be



excluded, of course, but this same gamble must be accepted even in the ideal situation of a rather clearly solitary lesion. The metastases could not have occurred after the eradication of the primary cancer (assuming this was actually accomplished), so, to speculate that metastatic foci, seeded just before the eradication of the primary cancer was effected, are present but not visible is uncomfortable, but serves only to engender a defeatist attitude. That courage in this regard can be rewarded by success is amply illustrated by the now famous case operated upon by Alexander [1], where successive lobectomies were performed for successively demonstrated metastases appearing bilaterally in a patient whose primary cancer was presumably (at the time of decision and in the hindsight of twelve* years quite certainly) controlled.

It is of course comforting to have several and preferably many months elapse after the primary operation before being called upon to

* Currently, twenty years

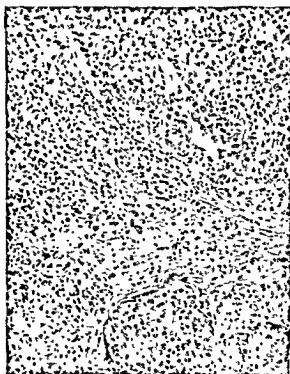
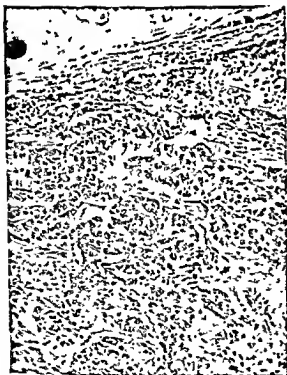


Fig 24-4 Illustrates the practical difficulty in clearly differentiating a metastatic cancer from a second primary cancer. A sixty-four-year-old female who ten years previously had undergone a right radical mastectomy for a poorly differentiated adenocarcinoma of the breast with axillary metastases (original slides not available) showed no evidence of recurrence. (Top) A right hilar shadow, discovered by routine roentgenography, had been present longer than one year. Total pneumonectomy was required because of the location of the tumor. (Bottom left) Histologically this tumor is again an adenocarcinoma. (Bottom right) Photomicrograph of a mediastinal lymph node that was invaded by a similar neoplasm. The point as to whether this lung lesion represents a metastasis from the breast or a second primary cancer can be debated. The evidence, however, seems to favor the latter opinion.



evaluate its adequacy preliminary to deciding for or against aggressive treatment of a secondary deposit. Such lapse of time is, however, not always afforded and the gamble must be taken if there is a reasonable chance that the primary cancer is controlled.

In Central and Endobronchial Location

Lesions located endobronchially are admittedly more difficult to reconcile as being metastases, unless they are accessible to bronchoscopic biopsy. Once the diagnosis of pulmonary metastasis is established or by differential studies strongly suspected, however, the same criteria of management outlined for the peripheral tumors are applicable.

CRITERIA OF MANAGEMENT IN SYNCHRONOUS LESIONS

The occurrence of a cancer at some extrapulmonary site, accompanied by a pulmonary lesion acceptable as a metastasis therefrom, poses a problem in management that is ex-

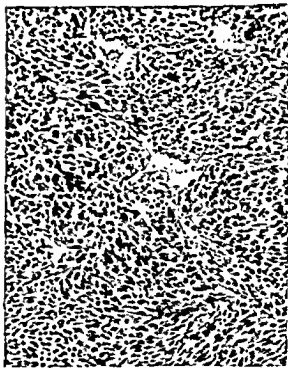


Fig. 24-5. Presents the problem of a second primary cancer in a sixty-one-year-old female who seven years previously underwent a left radical mastectomy for carcinoma (Top) Pulmonary symptoms of four months' duration led to the roentgenographic findings as depicted. (Bottom left) The neoplasm was resected by lobectomy. There was no gross mediastinal lymphadenopathy and the lymph nodes included in the specimen were negative for metastatic involvement. Photomicrograph of the original breast cancer, an adenocarcinoma. (Bottom right) Photomicrograph of the pulmonary neoplasm, which is a sarcoma and not related to the breast carcinoma.

ceedingly difficult to subject to any rules. If the lung lesion is metastatic, the overwhelming probability is that the primary cancer has already transcended the realm of operability or other chance at cure. In this respect, cancers of sarcomatous nature may offer a somewhat better outlook than the carcinomatous tumors, as will be elaborated upon later. If, however, the lung lesion is believed to be solitary, the primary neoplasm still should probably be explored with the idea of radical treatment. Should the prognosis seem reasonably good as a result of this procedure, the metastatic cancer may then be considered for treatment.

Contraindications to Surgical Exploration or Resection

Even though by original admission any consideration of resecting metastasis to the lung accepts virtually no contraindications to the performance of thoracotomy for this purpose, since by this means a chance at survival is offered instead of inevitable fatality, certain circumstances do not justify it. These include debilitating disease generally or advanced cardiac disease in particular, if these cannot be sufficiently well controlled to make survival of the required pulmonary resection likely.

Phrenic or recurrent laryngeal nerve paralysis usually denotes unresectability and therefore constitutes a contraindication. If such paralysis is known to have occurred very recently, particularly in the case of phrenic paralysis where the nerve is presumed to be invaded along the pericardium, resection conceivably may still be possible.

It should be pointed out that paralysis of the *left recurrent laryngeal nerve* usually means invasion of the hilus under the aortic arch, with great likelihood of unresectability. Involvement of the *right recurrent laryngeal nerve* usually signifies the presence of cancer in the root of the right neck, because the nerve on this side does not descend into the thorax. Thus, with intrapulmonary tumors located at any point, including the right apex where direct extension can involve this nerve, the presence of a paralyzed right recurrent laryngeal nerve is generally construed as a contraindication to exploration because of unresectability in the case of right apical tumors

where extrathoracic extension is probable, or because it is presumptive evidence of disseminated cancer when the demonstrated tumor is located elsewhere within the pulmonary field.

A *pleural effusion* is a relative contraindication in cases of known lung metastasis as it generally bespeaks pleural dissemination. The demonstration of tumor cells in the fluid makes the futility of surgical intervention certain.

OPERATIVE PROCEDURES FOR PULMONARY METASTASES

GENERAL CONSIDERATIONS

Any patient coming to operation for a solitary metastasis is presumed to be in good general condition because, otherwise, grave concern should be expressed that further neoplasm is in existence.

The approach to thoracotomy as generally used, and decidedly the one of my own personal preference, is through a posterolateral incision, entering the pleural cavity through the bed of a resected rib, with the patient lying in right or left lateral decubitus position. This provides for easy exposure and insures a secure closure of the thoracic cage (see Chap. 19).

CONDUCT AT EXPLORATION OF THE CHEST

The opened pleural cavity and its content should be explored by inspection and palpation in systematic fashion in order to determine as nearly as possible the nature of the lesion under investigation. The mediastinum should likewise be examined with particular reference to the possible presence of lymph node involvement.

Frozen-section examination of tissue obtained by excisional biopsy can usually be carried out in peripheral tumors and can be relied upon to differentiate between neoplasms and inflammatory processes, and similar examination of any suspicious mediastinal lymphadenopathy may be equally helpful. In this regard, it must be remembered that regions of pneumonitis often surround peripheral neoplasms, and such changes are constantly present distal to neoplasms producing bron-

chial obstruction. Care is therefore required to supply the pathologist with a specimen of actual tumor and not merely one from an indurated lung, for otherwise a correct verdict cannot be given. Differentiation of a primary from a metastatic tumor poses a very difficult problem for the pathologist.

The finding of nodules in the lung, other than the preoperatively recognized mass, is important and examination of one or more of these may readily corroborate the diagnosis of metastatic cancer even though it immediately renders an almost certainly hopeless prognosis.

EXTENT AND TYPE OF RESECTION TO BE UNDERTAKEN

The extent of resection that is to be done for lung metastasis is determined by the location of the tumor. The consensus seems to indicate local extirpation, basically [11]. Whereas this may be accomplished by wedge excision in favorably located peripheral neoplasms, lobectomy or pneumonectomy will be necessary in the more centrally placed tumors, particularly those situated endobronchially. The choice between a wedge excision and an anatomically more accurate segmental resection of less than a pulmonary lobe would seem to be dependent upon the location of the tumor with respect to accessible lung margins and/or intersegmental boundaries. Wedge excision is not well suited to neoplasms located along the broadly curving lung surfaces, being easiest to carry out in lesions at or near its sharper borders. Tumors located some distance subpleurally yet still within the lung periphery, insofar as general topographic considerations are concerned, likewise call for the more tedious but anatomically more accurate management by individual treatment of the arterial, venous, and bronchial radicals that supply the segment or segments involved.

The adequacy of pulmonary lobectomy as treatment for selected primary lung cancers has been suggested [3] and may well be the anatomic unit of excision adequate for metastatic nodules in lung, unless wider excision is required by the location of the tumor. No definite conclusions seem permissible on the basis of the rather meager data available for

analysis at the present time (see Chap. 22A).

On the other hand, how radical an attempt at extirpating extensive pulmonary or intrathoracic metastases one is justified in making must be determined by individual and personal considerations. The philosophic and moral implications involved are not to be considered here, because they require the determination of that point where courage ceases to be courage and becomes fruitless mutilation.

RESULTS

On the basis of collected reports, 15 to 16 per cent of patients who have been subjected to pulmonary resections for cancer metastatic to the lung have survived three years or longer. The operative mortality was 10 per cent [10].

It seems entirely justifiable to speculate that the figure for survival is low, and certainly a 10 per cent mortality rate for what should be uncomplicated pulmonary resection is high.

Both of these figures are based on material that covers a span of some twenty years. The natural evolution of the field of thoracic surgery has tended to highlight the early successes as well as dilute the early high rate of operative risk. The towering strength of the pioneer spirit is reflected throughout this whole scene.

The succeeding years will permit a factual statement on more accurate grounds than at present is possible as to three-year or five-year survival figures as more experience is collectively garnered. It is logical to say, however, that such a figure will be directly proportional to the care expended in selecting patients for treatment. On the other hand, a statistical result is not the goal of treatment; and resection of pulmonary metastases or the performance of exploratory thoracotomy for this purpose any time that there is reasonable chance that the pulmonary lesion is the only remaining bit of cancer is entirely justified under present-day concepts of management.

The risk of well-ordered exploratory thoracotomy is negligible and is but minimally increased for lobectomy. Pneumonectomy, when required, will carry a somewhat higher risk, particularly in the age group subtended by this discussion. The final figure for operative

risk will, however, probably represent a balance between the care exercised in selecting candidates on the one hand and the sensible admission of defeat at the operating table on the other.

The prognostic outlook seems better by a four to three margin for the solitary metastases arising from sarcomas as against carcinomas [1, 10]. Even though the volume of material is insufficient to permit valid conclusions, certain additive considerations may be called upon to reinforce such a contention.

(1) The greater general incidence of carcinomas as opposed to sarcomas suggests that the percentage incidence of truly solitary sarcomas is higher than occurs with carcinomas, since there are fewer examples of sarcoma to select from. (2) The predilection of carcinomas to spread by way of the lymphatics hints strongly at the conclusion that the presence of a carcinomatous pulmonary metastasis implies extension of the primary cancer beyond its immediate lymphatic barriers. Conversely, since sarcomas spread by preference through the blood stream, a ready avenue for the

deposition of multiple metastases in the lung is provided. Thus, an apparently solitary lung lesion under these conditions lends strength to the possibility that it is truly single, either because other metastatic seedings have not occurred or, if they have taken place, have failed to flourish.

Hypernephromas or renal cell carcinomas may share somewhat this same position with the sarcomas. One of the longest recorded survivals was an adenocarcinoma of the kidney [2].

Even though it is only during the very recent past that great interest has given strong impetus to work along these lines and the available data are at best fragmentary and sketchy, certain conclusions are obvious: (1) Cancer metastasizing to lung can be represented by a single deposit whose removal can lead to cancer-free survival of many years. (2) The bearer of a metastatic pulmonary cancer should be given the benefit of resection if there is any reasonable probability that the tumor in question is the one remaining bit of the cancer.

Radiation Treatment of Bronchogenic Carcinoma

Isadore Lampe

INDICATIONS AND CONTRAINDICATIONS FOR IRRADIATION OF LUNG CANCER

Various opinions have been expressed regarding the value of radiation therapy in carcinoma of the bronchus. Overholt stated that x-ray treatment had not yet produced a single cure and that inoperable cases were often made worse and survival shortened. Edwards [13] stated that x-ray therapy some years ago produced such general reactions as not to warrant submitting patients to treatment because so many were made more miserable than if left alone. Rienhoff [42] stated that radiation therapy is of no benefit.

At present, the basic indication for x-ray treatment of bronchial carcinoma is a negative one, namely, inoperability. This includes patients who are candidates for exploratory thoracotomy but who refuse operation, and those who on the basis of initial evaluation are also candidates for thoracotomy but the procedure is not done because of contraindications presented by other conditions (heart disease, etc.). In addition, there are patients who on clinical and radiologic evaluation are found to be suitable for thoracotomy but the operation demonstrates nonresectability; patients who present clinical or radiologic evidence of nonresectability but without extrathoracic metastases; and patients with extrathoracic metastases.

Of the diversity of situations included in the inoperability category, which should be chosen for radiation therapy? This question has been answered in different fashions by various workers. Huguenin and Fauvet have tried to treat all patients with inoperable lung cancers, without selection. Experience has taught them not to irradiate massive pulmonary carcinoma involving all of a lobe, since

massive tumor necrosis develops that may result in death. For palliative therapy they consider only a few contraindications to exist: anemia, cardiac failure, azotemia, and visceral metastases. Pohle and Siris [39] state that advanced cancer, general debility, and marked obstruction with infection contraindicate intensive therapy.

Hilton [17], Dobbie [12], Shorvon [44], Paterson [37], Paterson, Tod, and Russell [38], Mason [30], and Björk [6] consider the indications for radiation therapy from the point of view of patients who are candidates for radical treatment as opposed to palliative treatment. In general, radical treatment represents a serious effort to expose a limited volume of tissue embracing the tumor to a high total dose over a protracted time, with the aim of achieving elimination of the neoplasm.

The most elaborate study of the contraindications to radical irradiation has been made by Björk. Poor general condition of the patient and extrathoracic metastases are considered as absolute contraindications. Of thirty-five patients in poor general condition, nineteen were made worse by radical irradiation, sixteen dying within three months after the beginning of treatment. No change followed the treatment in seven, four dying within six months. Nine patients showed improvement but eight had died, seven within twelve months. Of thirty-eight patients who became worse during or after irradiation, the general condition at the beginning of treatment was bad in twenty-one and only fair in fourteen. Of thirty-four patients with extrathoracic metastases who received a course of deep x-ray treatment, thirty-one died and three were alive at six months or less; of those dead, only four lived as long as ten to twelve

months, the average survival being 4.2 months. Therefore, Björk believes that x-ray treatment is of no real value when extrathoracic metastases are present, except that in patients with severe pain such treatment may give relief; this applies chiefly to osseous metastases. A large pleural effusion (but not a small one) is also a contraindication; attempts to irradiate along with thoracenteses were ineffective. Of twenty-eight patients with large effusions, twenty-five were dead (only three surviving for ten to twelve months) and three were living but only at four to six months after treatment. Infection was not considered an absolute contraindication since in some cases it was possible to control it by preliminary treatment with penicillin.

Paterson, Tod, and Russell [38], reporting on the results of treatment at their institution, listed 474 patients with cancer of the lung and mediastinum. Of these, 157 were too far advanced to warrant any consideration of radiation treatment even though it was their belief that genuine palliation is obtainable by palliative irradiation. Of the 312 patients irradiated, the treatment was restricted to a palliative approach in 164, while 148 were treated radically. In 58 of the 312 patients irradiated, the primary focus of the cancer was thought to be in the mediastinum.

Of 179 patients with inoperable lung cancer seen by Hilton, 84 were too ill and the cancer too far advanced for x-ray treatment, 46 received palliative irradiation, 2 were treated postoperatively following pneumonectomy, and only 47 were considered candidates for radical radiation therapy. Shorvon reported on 213 patients of whom 75 were too ill and the cancer too far advanced for radiation treatment; 23 were given palliative irradiation, 4 were treated postoperatively, and 111 received radical therapy. Of Björk's 132 patients treated with x-ray, 95 were candidates for palliative treatment only, and 37 were radically treated. On the basis of these figures, it seems reasonable to estimate that radical radiation treatment can be undertaken in only about one third of the patients with inoperable lung cancer.

RADIATION TECHNICS

Currently the radiation treatment of bronchial carcinoma is carried out largely by ex-

ternal x-ray irradiation. Intraluminal radium therapy and interstitial implantation through a bronchus or at thoracotomy, tried in the past, have been abandoned, although recently renewed efforts in these directions have been made by Ariel and associates [2] (see Chap. 27).

Govaerts, Herve, and Ramioul [15] and also Brunnix [8] describe a technic of radium irradiation by means of radium tubes fixed in the distal end of a special, small-calibered, radiopaque sound. The sound is introduced through a bronchoscope and the position of the radium source is adjusted to the site of the tumor as determined bronchoscopically by fluoroscopic control. If complete bronchial obstruction exists, the radium rests on the upper pole of the tumor. Generally a 50 mg. source with a monel metal wall is used. Several hours of exposure are given daily with periodic fluoroscopic check on position. Total exposure was twenty hours or more. Of six cases cited, the longest follow-up was eight months; four of the six patients showed cicatricial bronchial stenosis at the site of irradiation from two to eight months after treatment, the stenosis varying from partial to complete. The disadvantage of this approach is the limited zone of adequate radiation intensity that can be achieved because of the rapid fall-off of dose with slight increase in distance from the radiation source. Only with unusually small tumors in a large bronchus would such a technic have any possibility of eradicating the cancer. Stenosis as a complication will occur with high frequency.

Most of the recorded experience deals with the use of x-ray generated in the 200 to 400 kv range; several reports on high-energy radiation treatment (one million volts or greater) have been published since 1944, such as those of Hocker and Guttmann [18], Williams [50], Nickson, Clifton, and Selby [32] and Haas, Harvey, and Melchor [16] (see Chap. 26). In general, the technics that have been used may be divided into two groups: (1) Multiple small fields with beams passing through each field, converging on the tumor region (with different workers the number of fields varies from eight up to twenty-four); with this technic, high dosage is aimed for in the tumor region; so-called

medical treatment. (2) Larger fields, usually about four in number, cross-firing the tumor volume, designed to deliver in this larger volume a smaller dose than in the small field techniques.

Winternitz and Smithers [52] use two sets of fields, one anterior and one posterior, each consisting of eight small fields that are arranged on a horizontal plane around the circumference of a circle which is usually 7 to 9 cm. in diameter. Four anterior and four posterior fields are treated each day and the beams are angled so the central rays intersect at a point on the far side of the tumor. The fields are small, circular, and most commonly 7 and 8 cm. in diameter. The angle of the beam to the horizontal is usually 55 to 65 degrees and is achieved by an axial beam director that defines the axis of the irradiated volume, the radius of the circle, and the angulation. Using 400 kv radiation, tumor doses of 5,000 to 6,000 r in five to six weeks have been given to tumors 7×8 cm. in diameter 8 to 10 cm. below the skin, with only a mild skin erythema.

Vogt [47] uses about fourteen fields, 6×8 cm. in size, distributed about the chest and back, including supraclavicular and axillary fields. Two to five fields are treated daily over an eight-week period to total surface dose of over 30,000 r. The individual dose per field is 200 r using 180 kv, 0.5 mm. Cu filter, and distance 40 cm. He advises that the tumor dose should not exceed 200 r per day, since too rapid regression results in complications. This technique has produced good remissions but in the limited material so treated to date recurrence always developed.

Shorvon [44] uses four small fields (6×8 cm. or 10×8 cm.), front and back, angled so that each beam envelops the tumor. Additional fields, front and back, can often be applied directly over the tumor so that a total of eight to ten fields may be used. The beams are angled by the pin-and-arc device (Dobbie). Treatment is carried out over a period of five to six weeks, treating six times weekly. He uses 190 kv, 0.5 mm. Cu, 0.5 mm. Al (h.v.l. 1.09 mm. Cu), F.S.D. 40 cm.

Roberts [43] described his technique as consisting of a double ring of fields, four in the central ring and eight in the outer ring. Two

such double rings, one on the front and one on the back, make twenty-four fields, which were sometimes supplemented by others on the homolateral side. Each field received about 1,200 r.

Kaplan and Etkin [24] reported four patients who were treated with eight to ten fields arranged in a band around the chest with angulation of the central rays determined by the use of the Demy protractor; 200 kv radiation of h.v.l. 1.9 mm. Cu was used at a distance of 50 cm. The daily dose was usually 300 r as measured in air to each of two fields, with total skin doses ranging from about 16,000 r to 24,000 r in 4.5 to seven weeks. All four patients were much improved at two to eight months after treatment, three having returned to work.

At the Holt Radium Institute [12,37,38], for radical treatment multiple small, circular fields, anteriorly and posteriorly, are employed. Following assessment of the position of the tumor, a complete plaster jacket of the thorax is made and the position of the tumor in space in this shell is determined by anteroposterior and lateral films. The distance from the site of each field on the shell to the tumor is determinable and available for calculations of depth dose and consideration of symmetry of radiation distribution, etc. Gaps between cone ends and the shell are filled in by seatings of "unit density" wax. Beam-directing devices are employed, such as the "back pointer," which defines the treating beam in position and direction by locating the points at which its central axis enters and leaves the surface of the patient. The objective with this technique is to deliver 6,000 r tumor dose in five weeks.

In the second group of techniques, consisting of fewer fields of larger size, it is usually stated that the objective is frankly palliative in the sense that it is conceded that the tumor volumes, nearly always large, cannot be brought up to a dosage level that is considered "cancericidal." These techniques are in general similar, consisting usually of about four fields with total dose per field of 2,000 to 3,000 r. Ott [34] uses three to five fields, 80 to 150 sq. cm., and gives individual doses of 75 to 150 r daily to one field to a total of 2,000 r (190 kv, filter 0.75 Cu and 0.5 mm.

Al, h.v.l. 1.2 mm. Cu, F.S.D. 40 cm.) per field. Huguenin and Fauvet [20] set up four cross-firing fields on a basis of frontal and lateral chest films: two fields on the anterior surface of the chest, one on the posterior surface, and an axillary field. At each sitting 200 r is given, treating four to five times weekly until 2,500 r per field has been administered. Mason [30] tries to give a tumor dose of 2,500 to 3,000 r in three weeks through four or five chest fields when little more than palliation is expected; in cases of mediastinal obstruction, a single dose of 500 r is given and supplemented as the patient's progress seems to indicate.

For postpneumectomy treatment, or if the tumor cannot be accurately localized, or if the tumor-bearing volume exceeds 8 cm. in linear dimension, Shorvon [44] uses four or five large fields that may vary in size from 7.5 × 15 cm. to 10 × 20 cm.; radiation is administered six times weekly until 3,000 r is given to each skin field in five to six weeks (190 kv, 0.5 mm. Cu and 0.5 mm. Al filters, h.v.l. 1.09 mm. Cu, F.S.D. 40 cm.).

For patients in whom various factors do not permit the use of radical treatment through small fields to a dose in the tumor of 6,000 r in five weeks, Paterson [37] uses a variety of approaches. If the radiographic appearance is that of an "early or moderately early bronchial carcinoma" (this is defined as atelectasis of either one lobe or of a whole lung or a hilar shadow of limited size) but the patient's age makes a long-term course inadvisable, a short course but still radical in technic is given in eight days, achieving a tumor dose of 4,500 r. If the chief feature of the radiographic appearance is deformity and enlargement of the mediastinal shadow, a technic of treatment termed "regional therapy" is employed to expose the entire mediastinum to a dose of about 3,000 r in seventeen days. Large fields (three or four) are used, 20 × 25 cm. long and 10 × 12 cm. wide. In the late cases (massive lung involvement, multiple pulmonary lesions, large effusions, all patients in poor general condition or aged, all patients with extrathoracic metastasis), prolonged or radical treatment is considered useless. Paterson believes that all the palliation possible can be obtained by simple

radiation treatment. A single session, irradiating the most affected region by two large fields (anterior and posterior) to a skin dose of 1,000 to 1,250 r, is considered as useful as more elaborate procedures. Also, he has used a four-day course, treating once daily, delivering 2,500 r skin dose through two fields, one anterior and one posterior. Where the hilar bronchial cancer seems dominant in causing symptoms, multiple small or medium fields directed toward the hilus without elaborate beam direction and giving a tumor dose of over 2,000 r in four days, has proved useful and evoked minimal reaction and general upset.

Pohle and Siris [39], using 400 kv, h.v.l. 2.4 mm. Cu, treat two chest fields daily (anterior and posterior, 10 × 10 cm. to 15 × 15 cm. in size) at the rate of 200 r per day to a total of 2,400 r per field, or 150 r per day to a total of 3,000 r per field. A second course is administered three months later: 1,600 to 2,000 r per field at 200 r per day to both fields, or 1,500 to 1,800 r per field at the rate of 150 r per day. Further irradiation is then given in small amounts not less than three months apart for control of symptoms, metastases, or increased tumor size. With advanced disease, general debility, or marked obstruction with infection, the treatment schedule just described, which is termed "intensive therapy," is considered contraindicated; in such cases, 800 to 1,600 r are given to each field, at a rate of 200 r per day to both fields. If response is satisfactory, more intensive treatment is given in six weeks; otherwise, short cycles are repeated at intervals of not less than three months as indicated.

Leddy states that in a group of selected patients in fairly good general condition he has given 3,000 r to each of four chest fields, cross-firing the tumor, using 200 kv with a filter of 2 mm. Cu equivalent at a distance of 50 cm.; the results were poor and the treatment was not well tolerated. Consequently, he abandoned doses larger than 1,500 r per field, preferring to use total doses to each of the four fields of 500 to 750 r (200 kv radiation filtered through 0.75 mm. Cu and 1.0 mm. Al, F.S.D. 50 cm.), administering the course in four days. When the patient is in better-than-average condition, 1,000 r per field in sixteen

days is given. With cachexia or fever, 250 to 500 r may be given through anterior and posterior fields. If the physical condition is very poor or if there is any suspicion of lymphoblastoma, he uses 130 kv.

In general, both for radical and palliative treatment technics, high-energy radiation (one or more million volt x-ray, cobalt-60 radiation, or betatron x-ray radiation) will simplify technical methods [16, 32]. Fewer converging fields are required, making for greater accuracy. Indeed, the simplest arrangement of two fields, one anterior and one posterior, will often suffice to deliver the desired dose in the tumor. Multiple cross-firing fields can reduce the magnitude of the dose in the normal tissues anterior and posterior to the site of the tumor; the logical extension of this is the use of a rotational technic to place a cylindric volume of high dose at the tumor site. This is applicable only when there is at least relative limitation in size of the suspected or proved volume harboring the tumor. With the patient in the horizontal position and a rotating source, this technic can be the simplest and most accurate for daily set-up. Such experience as has been obtained does not suggest that high-energy radiation will materially alter the accomplishment of radiotherapy in this disease. It does offer simplified technic, diminished or no skin reaction, and some degree of greater constitutional tolerance [9, 48] (see Chap. 26).

TUMOR DOSE

The following information is found in the literature regarding the "tumor dose" given in the x-ray treatment of bronchial carcinoma. Smithers states that his technic permits giving regularly a tumor dose of 5,000 to 6,000 r in five to six weeks to tumors 7×8 cm. in diameter at a depth of 8 to 10 cm. below the skin with the production of only a mild erythema. Dobbie speaks of a dose of 6,000 r in five weeks or an equivalent dose in a shorter time. Paterson, of the same institution, also prescribes 6,000 r in five weeks and 4,500 r in eight days as a useful compromise when age militates against a long-term course. In advanced cases with large mediastinal nodes, 3,000 r is delivered as a tumor dose through three or four fields in seventeen days. Mason

cites a tumor dose of 5,500 r for epidermoid tumors and 4,500 r for undifferentiated growths given in five to six weeks through four or five fields, whereas when only palliation is anticipated, 2,500 to 3,000 r in three weeks is considered sufficient. Shorvon also aims for a dose of 5,500 r in five or six weeks.

Appreciation of the magnitude of discrepancy that may be introduced by applying depth dose figures obtained from the usual type of phantoms to lung tissue is given by data published by Innes. Using a piece of lung 5 cm. thick, aerated to a pressure representing the mean negative pressure to which it would be subjected in the living body, the transmission of radiation through this specimen compared to that through water of the same depth was 1.47 for radiation h.v.l. 1.0 mm. Cu, 1.43 for h.v.l. 1.5 mm. Cu, and 1.32 for h.v.l. 9.3 mm. Cu (1,000 kv). The rates obtained for a 3.5 cm. thick section of a vertebral body (0.93 for h.v.l. 1.0 mm. Cu, 0.95 for h.v.l. 1.5 mm. Cu, and 0.98 for h.v.l. 9.3 mm. Cu) and for a 0.55 mm. thick section of rib (0.91 for h.v.l. 1.0 mm. Cu, 0.925 for h.v.l. 1.5 mm. Cu, and 0.98 for h.v.l. 9.3 mm. Cu) are also pertinent since the x-ray beams will traverse such structures in the treatment of bronchial carcinoma. Thus, on one hand aerated pulmonary tissue allows greater transmission and the osseous structures reduce transmission, at least for the lower voltages. It is literally impossible to determine the result of the algebraic summation of these deviations. At best, the currently quoted "tumor doses" must be considered as crude approximations with a considerable inherent error, and treatment schedules based solely on this parameter of dosage may be falsely founded. Beyond this, one should protest against the not uncommon current custom of quoting a "tumor dose" that is the summation of the contributions of the cross-firing beams at only a single point in the estimated tumor volume, usually its center. It is the distribution of dose magnitude throughout the tumor volume that is important, since underdosage at any point is crucial. If one recalls the lack of accurate knowledge regarding the true extent of these neoplasms, single point "tumor doses" more often than not will

show no correlation with results of therapy. Description of radiation dose by "tumor dose" in some hands constitutes a sincere attempt to establish one parameter of true tissue dose, whereas in others it represents an easy solution for radiation therapy, equating the latter solely to the computation and administration of a certain "tumor dose." Desirable and important as a knowledge of the true radiation dose in carcinoma of the lung certainly is, its determination still represents an objec-

adenocarcinoma was radioresistant. Steiner [46], on the basis of histologic studies, found the small, undifferentiated carcinoma with dark hyperchromatic nuclei and scanty cytoplasm to be highly radioresistant and considered that perhaps the squamous-cell carcinoma of the lung could eventually be added to the list of squamous-cell carcinomas curable by radiation therapy. Bariéty, Delarue, and Paillas [4] stated that squamous-cell carcinoma of the bronchus was feebly radio-



Fig 25 1. (Left) Roentgenogram of a thirty-four-year-old male showing a right paratracheal mass and another mass over the upper right cardiac margin. Using 200 kv (h.v.l. 1.0 mm Cu) radiation at a distance of 50 cm, a test of irradiation was carried out, 400 r (air) to each of four cross firing fields. (Right) Roentgenograms two months later showed complete regression of the masses, therefore, a provisional diagnosis of lymphoblastoma was entertained. The patient died seven months later. At necropsy a poorly differentiated carcinoma of the left main bronchus with disseminated metastases was found.

tive that remains to be achieved and not one that has already been successfully accomplished.

GENERAL CONSIDERATIONS OF RADIOBIOLOGY OF BRONCHIAL CARCINOMA

Such data as exist on the radiosensitivity of this cancer are conflicting. Pohle and Siris [39] state that their best response (in terms of duration of survival to death) was obtained in squamous-cell carcinoma, Grade III, and that

sensitive and that the small-cell carcinoma was the most radiosensitive. Holmes [19] reported the oat cell and the undifferentiated varieties as the most radiosensitive. Leddy's report of five patients with adenocarcinomas surviving five or more years is interpreted by Poulet, in a study of correlation of histology and radiosensitivity, as suggesting a belief by Leddy that the glandular carcinomas are the more sensitive. Leddy, however, makes no explicit statement to this effect, claiming in 1947 [26] that radiologists know less about the



Fig. 25-2. A, Roentgenogram of a sixty-eight-year-old white male with a fungating tumor on the anterior lateral aspect of the right upper-lobe bronchial orifice. Pathologic diagnosis: noncarnifying squamous-cell carcinoma. B, The patient received 3,000 r (air) to each of four cross-firing 14×9 cm. fields (200 kv, h.v.l. 1.0 mm. Cu) at a distance of 50 cm. At the end of irradiation, two months later (1/8/47), virtually complete regression was noted. The patient was asymptomatic and gained weight until August, 1947, when cough recurred. C, Chest roentgenogram fifteen months later, demonstrating recurrence. Patient died two years after irradiation, and necropsy confirmed the diagnosis.

radiosensitivity of bronchial adenocarcinomas and squamous-cell epitheliomas than about similar tumors elsewhere in the body. Huguenin and Fauvet [21] do not consider that the tumor histology gives insight into the indication for radiation treatment. They point out that many tumors are difficult to classify, that the histopathology has been found to differ at autopsy from that in the bronchoscopic biopsy, and that it can be mixed in character both in the primary tumor and its metastases (this has been noted by Rhein-

gold, Ottman, and Konwaller [41] and by others).

Most bronchial carcinomas show a definite, often pronounced radiosensitivity. Indeed, a few cases have been encountered in our own experience in which large masses of mediastinal nodes melted away under small doses as rapidly and as completely as lymphoblastomas and carried such a presumptive diagnosis until autopsy revealed a carcinoma of bronchial origin (Figure 25-1). Although usually this extremely sensitive response was correlated with anaplastic tumors, including the small-cell variety, there is also evidence of radiosensitivity of the squamous-cell tumors in our cases (absence of the bronchial tumor on

postirradiation bronchoscopy and disappearance of mediastinal metastases on post-treatment radiographic examination (Figure 25-2). Additional evidence for radiosensitivity of the squamous-cell carcinoma is found in the fact that this tumor variety is predominant among the patients showing the best long-term results.

Infection is commonly associated with these

neoplasms, with abscesses and suppurative pneumonitis developing distal to the site of bronchial obstruction. Under conditions of vigorous radiation reaction, itself an intense inflammatory process, infected segments of lung can become gangrenous, leading to a fatal outcome. With heavy tumor infiltration of lung, of the walls of large mediastinal blood vessels, and of the esophagus, regression of tumor tissues may not be associated with an adequate reparative process of the infiltrated normal tissue; hemorrhage, abscess formation, mediastinitis, or pericarditis may follow. Pulmonary tissue is susceptible to radiation pneumonitis which, healing by fibrosis, impairs the pulmonary functional capacity; such fibrosis, if sufficiently severe and if it involves a sufficient volume of lung tissue, is incompatible with survival. In contrast to carcinoma of the cervix, for example, the handicap imposed by the nature of the tumor bed in bronchial carcinoma is severe.

It appears clear that the protracted administration of x-ray radiation offers the greatest benefit in overcoming the handicaps of the tumor bed by producing a slow diminution of the neoplastic tissue [1]. Nevertheless, informative data on dose-time relationships for this cancer are essentially negligible, except for the bare facts embodied in the techniques currently employed; likewise, with respect to the optimal daily dose in the tumor, little information exists. Vogt [47] recommends an average daily dose of somewhat more than 150 r and points out that daily tumor doses greater than about 200 r are poorly tolerated in that the tumor tissue may recede too rapidly and complications may follow. Hilton insists that satisfactory results can be achieved only if the therapist makes a daily examination of the patient, studies temperature, pulse, and respiratory charts, and adjusts the daily dosage to the clinical response.

RESULTS OF RADIATION TREATMENT OF PULMONARY TUMORS

A most striking development are the reports of a small group of patients with histologically verified cancer of the bronchus in which survival for five years was attained.

Björk [6] reported a patient with squamous-cell carcinoma alive and well five years and

one month after radical small-field x-ray treatment. Smithers [45] stated that a patient with squamous-cell carcinoma treated in September, 1940 was alive and well at the time of the report (April, 1949). Dobbie [12] had one patient, diagnosed histologically as having a squamous-cell bronchial carcinoma, alive and well five years after radical x-ray treatment. Paterson, Tod, and Russell [38] reported four patients with histologically proved neoplasms surviving five years. Zaunbauer [53] reported a forty-year-old patient in whom bronchoscopy demonstrated complete bronchial occlusion by a tumor; microscopic examination disclosed a small, round-cell carcinoma. Following irradiation, the patient improved and was completely symptom-free five years later.

In addition to these eight histologically verified cases, the following reports are of interest: Mason [30] reported two patients alive, one at five years, the other at 5.5 years after irradiation. It is not clear from his article whether the diagnoses in these cases were verified histologically. Widmann [49] reported one patient alive six years after irradiation. Repeated postirradiation bronchoscopies were negative but the patient suffered from a dry, hacking cough; it is not clear from the report whether a histologic report had been obtained. F. Robert [43] reported one patient with typical radiographic and clinical findings of a bronchial carcinoma, but whose biopsy was inconclusive, to be alive and well six years after treatment. Smithers [45] treated one patient in May, 1939, who died seven years later, in April, 1946, allegedly of a metastasis; it is not clear whether a histologic diagnosis was obtained.

Paterson, Tod, and Russell [38] cite three patients with clinical diagnoses of bronchial carcinoma who survived five years. Williams, using a 1,000 kv x-ray beam, treated a patient immediately after pneumonectomy. The patient had a squamous-cell carcinoma which at operation was found to involve the left pulmonary vein and the stump of this structure was left behind. The patient was alive and well five years later.

Leddy reported that of 125 proved cases, five patients survived five or more years. In the initial report in 1940, it is stated that three



Fig. 25-2. A. Roentgenogram of a sixty-eight-year-old white male with a fungating tumor on the anterior lateral aspect of the right upper-lobe bronchial orifice. Pathologic diagnosis, noncornifying squamous cell carcinoma. B. The patient received 3,000 r (air) to each of four cross firing 14×9 cm fields (200 kv, h.v.l. 1.0 mm. Cu) at a distance of 50 cm. At the end of irradiation, two months later (1/8/47), virtually complete regression was noted. The patient was asymptomatic and gained weight until August, 1947, when cough recurred. C. Chest roentgenogram fifteen months later, demonstrating recurrence. Patient died two years after irradiation, and necropsy confirmed the diagnosis.

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A considerable handicap to successful radiation therapy of bronchial carcinoma is found in the character of the tumor bed. Pulmonary infection is commonly associated with these



volume and that irregularities in the shape of the tumor-bearing volume obviated the possibility of uniform distribution of radiation dose. Total doses to each field varied from 2,000 to 3,600 r (air) with a daily rate of 150 to 200 r to two fields; 200 kv radiation of h.v.l. 1 mm. Cu was used at a distance of 50 cm. At the present time, all of the fifty patients are dead. Twelve per cent lived beyond one year and 2 per cent lived beyond two years. The longest survival was thirty-five months. Some degree of amelioration of symptoms was obtained in twenty-two patients. This varied from diminution of cough and chest pain for short intervals to significant gain in weight and strength and return to a normal state of health in a few for periods of over one year.



Fig 25-4. A Chest roentgenogram of a fifty three-year-old male with a carcinoma causing compression of the lower third of the trachea. The right main-stem bronchus was almost occluded by submucosal neoplastic infiltration. Pathologic diagnosis: small-cell poorly differentiated carcinoma. A roentgenogram of the chest revealed atelectasis of the right upper lobe and elevation of the right leaf of the diaphragm (phrenic paralysis). From 5/3/48 to 6/8/48, 2,350 r (air) was delivered to each of four chest fields cross-firing the mediastinum (200 kv, h.v.l. 1.0 mm. Cu) at 50 cm. B, C Radiographic and clinical improvement followed (roentgenograms taken 5/24/48 and 7/21/48). All signs of respiratory embarrassment and mediastinal obstruction disappeared. The patient felt well and returned to work, but symptoms recurred and he died four months postirradiation.

large, bloody pleural effusion, etc.

All fifty patients received x-ray treatment, given usually through four moderate-sized fields with the beams converging in the main mass of the neoplasm. Often, from the knowledge gained of the intrathoracic extent of the cancer, it was evident that all the neoplastic tissue could not be included in the irradiated

Shorvon [44] reports that of 213 patients seen, 75 were too ill and the cancer too far advanced for treatment; 23 were given palliative treatment, 4 postoperative irradiation, and 111 radical irradiation. In the nonirradiated patients, the average duration of life was 40 days after admission to the hospital; in the palliated group, the average duration

were still alive ten, 10.5, and twelve years after treatment. In each of the five patients the histologic type was adenocarcinoma. Pohle and Siris [39] doubted that these cases were acceptable as five-year survivals of bronchial carcinoma since it had been shown that it was difficult in a bronchoscopy biopsy to differentiate a carcinoma from an adenomatous growth. Our own experience with two patients with adenomas of the cylindromatous

prolongation of life, although one cannot be certain of the comparability of the cases in each series. Leddy and Moersch [28] also reported 125 untreated patients with none surviving one year. Boyd [7], reporting the experience with treatment of lung cancer at the Lahey Clinic, stated: "To our surprise two patients who were given x-ray therapy only lived for five years or longer."

The character of the material that is usu-



Fig. 25-3. A Chest roentgenogram of a sixty-three-year-old male in whom a bronchoscopy revealed a tumor in the lower part of the trachea, extending into the trachea from the right-stem bronchus; the carina was observed. Pathologic diagnosis poorly differentiated carcinoma. From 7/12/46 to 8/16/46, 3,130 r (air) was given to each of two anterior chest fields and 3,000 r to each of two posterior fields through 15 X 12 cm. fields (200 kv, h.v.l. 10 mm. Cu) at a distance of 50 cm. A roentgenogram one week prior to treatment showed right paratracheal adenopathy, right hilar and lower-lobe parenchymal densities. B. Two days before completion of treatment, the chest appeared almost normal. Five months later, right-sided pleural effusion and atelectasis developed, and the patient died in May, 1947. This is a typical course: radiographic evidence of regression with a variable degree of clinical improvement but early death.

variety in the trachea suggests that some adenomas may be radioresponsive although eventual recurrence is the usual outcome; one patient was followed for eleven years before the recurrence appeared.

Despite the advance demonstrated by the five-year survival of apparently authentic cases of bronchial carcinoma after radiation treatment, the over-all picture of accomplishment by irradiation of this cancer remains a gloomy one (Figures 25-3 and 25-4). Widmann [49] reported that among 119 untreated patients, none lived as long as one year after the diagnosis, while eighteen of 167 treated patients lived twelve months or more (five lived two to six years). These data suggest

ally encountered by the radiation therapist is exemplified by a series of fifty patients with bronchial carcinoma referred to our department for treatment. Analysis of this group showed that one refused operation; fifteen had exploratory thoracotomy and their cancers were found to be nonresectable because of mediastinal or other extrapulmonary extension; one patient was not explored because of the presence of an aortic aneurysm. In the remaining thirty-three there was obvious clinical, radiographic, or bronchoscopic evidence of inoperability: mediastinal metastases, carinal and tracheal involvement, recurrent laryngeal and phrenic nerve paralysis, esophageal invasion, rib invasion and destruction,

Treatment of Inoperable Carcinoma of the Lung with High-Energy Irradiation

Ruth J. Guttmann

This chapter discusses the advantages, accomplishments, and limitations of treating inoperable lung cancer with ionizing radiation generated at high energies (supervoltage 1,000 kv and higher; cobalt-60 teletherapy, and betatron).

It is the goal of any radiotherapeutic program to deliver a high dose of radiation to the neoplasm with minimal effect upon the normal contiguous structures. Irradiation in the higher energy range can accomplish this better than irradiation in the orthovoltage range. The technical factors inherent in the various high-energy irradiation sources, i.e., supervoltage roentgen irradiation, radium and cobalt-60 teletherapy, and the betatron, are discussed in Volume I. Suffice it to state here that the major advantages of the high-energy irradiation are that a much greater depth dose can be obtained with a minimal effect upon the overlying skin, any overlying bone, and with an almost negligible systemic reaction.

The advantages of high-energy radiation therapy, however, are of clinical value only if the cancericidal effects are equal to or better than that of ionizing irradiation of other wave lengths. Studies on the biologic effects of high-energy irradiation are being conducted but are not conclusive. It does appear that the biologic effect on cells is essentially the same as that achieved with 250 kv x-rays.

The following discussion is based on the author's personal experience at the Francis Delafield Hospital, Columbia University College of Physicians and Surgeons, New York.

TECHNIC OF IRRADIATION

In planning of treatment, accuracy of delivering the irradiation to all parts of the

cancer is of utmost importance. Accordingly, every diagnostic method that will help to determine the size and location of the neoplasm is utilized. Even a near miss would impair the result.

Contours are taken with narrow strips of wet plaster of Paris over the center of the region to be treated and the contours are traced on paper as soon as the plaster has hardened (Figure 26-1). With the help of anatomic cross sections and roentgenograms, normal organs and the tumor site are drawn into these cross sections that bear the actual measurements of the patient. The next steps include the determination of the field size and the calculation of the tumor dose. Adjacent normal, healthy structures are avoided as much as possible, which is feasible with supervoltage therapy.

Figure 26-2 shows a cross section of a



Fig. 26-1. Tracing of chest contour. (From R. J. Guttmann [1], courtesy Cancer.)

was 4.5 months. Of the 111 radically treated patients, 83 were dead at the time of the report (10 per cent survived more than one year, the longest survival being 30 months) and 28 (17 proved by biopsy) were alive. Sixteen of the living had received their treatment at least 6 and up to 36 months before (9 of the 16 had histologic proof of the diagnosis).

Dobbie [12] reported 170 patients of whom 111 (advanced cases) received palliative treatment, with large fields and low doses. Although symptomatic relief was often striking and in some degree occurred in 40 per cent of the patients, the duration of life was short, only 5 patients living beyond 12 months (maximum, 20 months). Of 59 patients treated radically, 48 were dead; 21 per cent lived beyond 12 months (maximum, 27 months). Of the 11 living patients, survival after treatment had ranged from 9 months to 6 years. In 6 of the 11, biopsy confirmation of the diagnosis had been obtained. One patient, without histologic confirmation of the diagnosis, showed recurrence at 9 months; another patient, with histologic confirmation, was showing a recurrence at 3.5 years. Dobbie suggests that it might be justifiable and preferable to exclude from treatment the late cases of proved carcinoma.

Bjork [6] studied 92 patients without extra-

thoracic metastases; 37 were treated radically (tumor dose of 4,000 r or more). At the time of the report, 16 were living: 8 less than one year after treatment, 5 at one to two years, one at three years, and one at five years and one month. Sixteen patients had died, the range of survival being three months to two years. In 9 patients symptoms were completely relieved, and 19 showed amelioration of symptoms. Of the 55 patients who were treated palliatively (tumor dose less than 4,000 r), 52 were followed; 45 had died from two months to 1.5 years after treatment; 7 were alive from 3 months to 1.25 years. Complete relief of symptoms was obtained in only one patient but palliation of symptoms occurred in 23 patients.

The conclusion that may be developed from these data is that x-ray treatment, in *properly selected cases* of bronchial carcinoma, can produce significant palliative results in the sense of amelioration of symptoms and prolongation of life. Indiscriminate use of x-ray treatment obscures the benefits that may be gained in the suitable case. Beyond palliation, the recent experience demonstrates that isolated instances of survival for five years or more without evidence of cancer can be achieved under certain conditions.

thorax that contains a lung cancer. The two opposing fields through which treatment with the 2,000 kv unit is to be given are shown. With this arrangement, the desired tumor dose of 6,000 r with a skin dose of 7,150 r is delivered. The spinal cord and the opposite lung are not in the path of irradiation. A dose of 5,000 r to 6,000 r to the lung causes complete fibrosis, which renders it afunctional. Hence, every effort must be made to save the remaining lung, as the survival of

ventional high-voltage units will, therefore, be an approach through multiple fields, either stationary or by rotation (Figure 26-4), which does not affect the normal skin excessively. A considerable amount of irradiation to the opposite lung and the spinal cord, however, is delivered.

The cobalt-60 unit, operating at a source-tumor distance of 75 cm., is shown in Figure 26-5. This radiation source does not permit as easy and efficient an approach as the 2

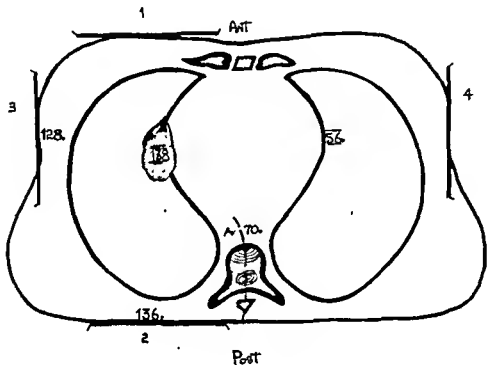


Fig. 26-4 Cross section through thorax. Field arrangement and dosage with 250 kv unit, four ports, 10 X 10 cm. Dose air, 4,400 r; skin, to ports 1 and 2, 5,980 r, and to ports 3 and 4, 5,630 r, tumor, 6,000 r. (From R. J. Guttmann [1], courtesy Cancer.)

the patient depends not only on the elimination of the cancer but also on the proper functioning of the other, normal lung.

A comparison with Figure 26-3 will emphasize this point. It shows the same neoplasm of the lung illustrated in Figure 26-2 but it demonstrates clearly that the same approach of two opposing fields is not possible with the conventional 250 kv unit. In order to deliver a tumor dose of 6,000 r, it would be necessary to give a skin dose of 10,000 r, which is more than normal skin can endure. The only possible solution for the problem of delivering 6,000 r to the tumor with con-

ventional high-voltage units will, therefore, be an approach through multiple fields, either stationary or by rotation (Figure 26-4), which does not affect the normal skin excessively. A considerable amount of irradiation to the opposite lung and the spinal cord, however, is delivered.

Rotation therapy or scanning is undesirable in treating most pulmonary neoplasms, especially those of the periphery of the lung, because excessive amounts of the healthy neighboring tissue are exposed to irradiation unnecessarily; for example, the spinal cord and the hilus of the opposite lung (Figures 26-6 and 26-7).

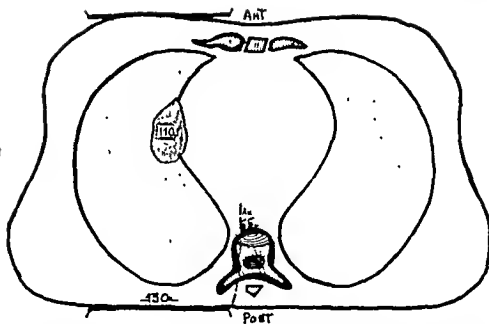


Fig. 26-2. Cross section through thorax. Field arrangement and dosage with 2,000 kv unit, opposing ports, 10×10 cm. Dose: air, 3,500 r, skin, 7,150 r, tumor, 6,000 r. (From R. J. Guttmann [1], courtesy Cancer.)

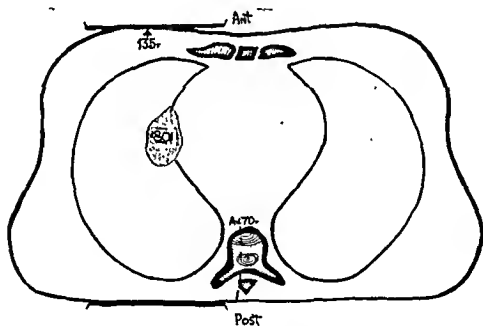


Fig. 26-3. Cross section through thorax. Field arrangement and dosage with 250 kv unit, two ports, 10×10 cm. Dose: air, 6,000 r, skin, 10,000 r, tumor, 6,000 r. (From R. J. Guttmann [1], courtesy Cancer.)

FACTORS OF IRRADIATION

A daily tumor dose of 200 r is usually given. The majority of the patients have received a total tumor dose of 5,000 r to 6,000 r in a five-week to six-week period. The physical factors that remain constant are the 2,000 kv machine, a target-skin distance of 100 cm., filtration of 4 mm. of lead, and a half-value layer of 7 mm. of lead. If the cobalt-60 teletherapy unit is used, a source

RELATIONSHIPS OF CLINICAL RESPONSE TO POSTIRRADIATION ROENTGENOGRAPHIC ALTERATIONS

The majority of patients showed relatively little roentgenographic change. Obviously, large tumors, which often have already caused many changes in surrounding tissues, do not melt away under radiation therapy. In addition, radiation pneumonitis, pleurisy, and later fibrosis appear frequently, persisting for the

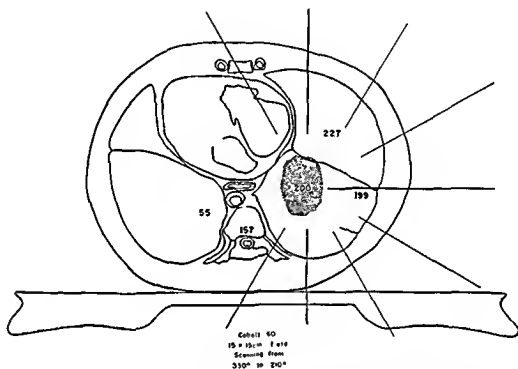


Fig 26-7. Cross section through thorax. Field arrangement and dosage with cobalt-60 unit, scanning from 330 degrees to 210 degrees, showing that the spinal cord and opposite hilar region still receive a high dose. (From R J Guttman [2], courtesy American Journal of Roentgenology, Radium Therapy and Nuclear Medicine)

2 cm. in size and a source-tumor distance of 75 cm. are utilized.

Before starting therapy, localization films are taken with the treatment unit while the patient is in the proper treatment position, because only these films will assure us that the size and position of the outlined field correspond with the region intended for irradiation.

Figure 26-8 left shows the routine chest roentgenogram of a patient with a large cancer in the left upper-lung field, and Figure 26-8 right the localization film.

duration of the patient's life. How much, therefore, of the original tumor shadow remains is impossible to determine by subsequent follow-up roentgenologic studies.

Complete disappearance of the tumor after radiation therapy has been observed rarely. One fifty-four-year-old patient with a five-month history of cough, hemoptysis, and weight loss presented a large mass in the right lower lobe (Figure 26-9, left) for which an exploratory thoracotomy was performed. The tumor, histologically diagnosed as carcinoma, had invaded the parietal pleura and the

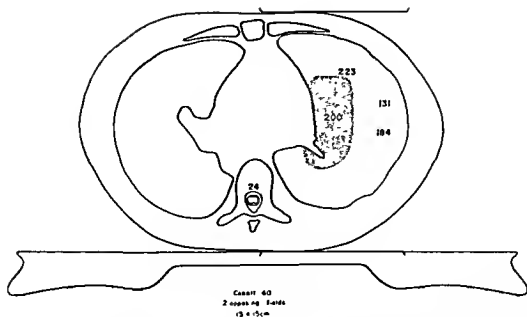


Fig. 26-5. Cross section through thorax. Field arrangement and dosage with cobalt-60 unit, opposing 15×15 cm. ports. (From R. J. Guttmann [2], courtesy American Journal of Roentgenology, Radium Therapy and Nuclear Medicine.)

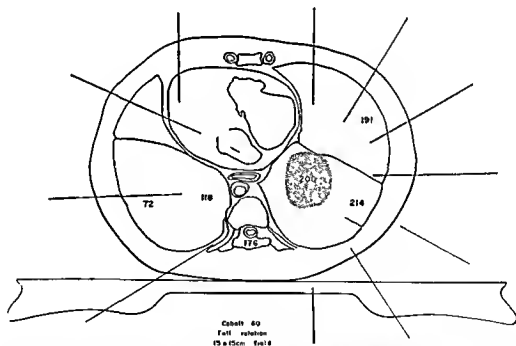


Fig. 26-6 Cross section through thorax. Field arrangement and dosage with cobalt-60 unit, full rotation, demonstrating the high dosages delivered to spinal cord and opposite hilar region. (From R. J. Guttmann [2], courtesy American Journal of Roentgenology, Radium Therapy and Nuclear Medicine)

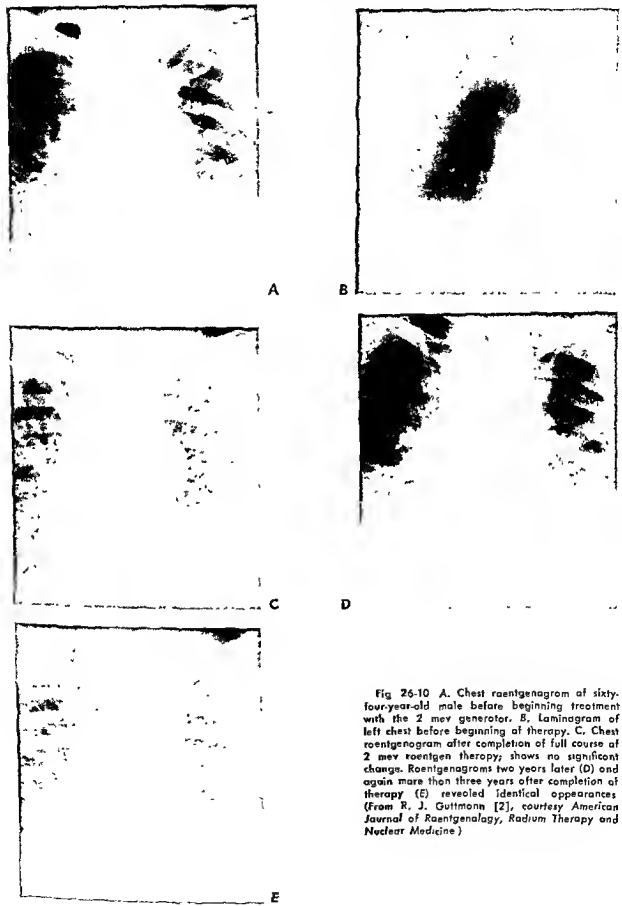


Fig 26-10 A. Chest roentgenogram of sixty-four-year-old male before beginning treatment with the 2 mev generator. B. Laminogram of left chest before beginning of therapy. C. Chest roentgenogram after completion of full course of 2 mev roentgen therapy; shows no significant change. Roentgenograms two years later (D) and again more than three years after completion of therapy (E) revealed identical appearances (From R. J. Guttmann [2], courtesy *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*)



Fig. 26-8. (Left) Routine chest roentgenogram of a patient with a large lesion in the left upper lung field. (Right) Localization film. (From R. J. Guttman [1], courtesy Cancer.)

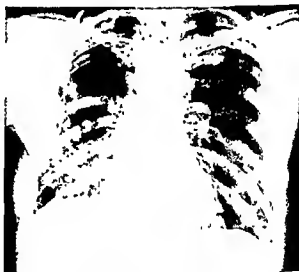


Fig. 26-9. (Left) Chest roentgenogram of fifty-four-year-old male with carcinoma of the right lung before beginning of treatment with the 2 mev generator. (Right) Roentgenogram four months after completion of therapy. Complete disappearance of tumor. Patient now asymptomatic, four years later (From R. J. Guttman [2], courtesy American Journal of Roentgenology, Radium Therapy and Nuclear Medicine.)

pericardium, and was deemed to be inoperable. He was treated with the 2 mev generator, receiving a tumor dose of 5,800 r in six weeks. He tolerated the treatments well and all symptoms disappeared. Figure 26-9 (right) shows complete disappearance of the tumor four months after termination of the therapy. The patient is asymptomatic now, four years later, and works full time.

The lack of dramatic changes in the

roentgenograms is not necessarily a poor prognostic sign. Figure 26-10A represents a chest roentgenogram of a sixty-four-year-old patient who complained of weakness, cough, and clubbing of his fingers for four months prior to the examination. A chest roentgenogram revealed a large mass in the anterior mediastinum associated with a diffuse haze occupying the left lower lung field. The mass was better revealed in a laminogram (Figure

RESULTS

All 144 patients who were evaluated had their diagnoses verified microscopically (Table 26-1). Carcinoma without further histologic specification was present in 58 patients, squamous-cell carcinoma in 44 patients, undifferentiated carcinoma in 20, adenocarcinoma in 13, oat-cell carcinoma in 5, thymoma in 2, and mesothelioma in 2.

TABLE 26-1 —RADIATION THERAPY OF INOPERABLE LUNG CANCER: MICROSCOPIC CLASSIFICATION

Microscopic classification	Number of patients
Carcinoma (unclassified)	58
Squamous-cell carcinoma	44
Undifferentiated carcinoma	20
Adenocarcinoma	13
Oat-cell carcinoma	5
Thymoma	2
Mesothelioma	2
Total	144

SOURCE: R. J. Guttman [2], courtesy *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*.

A high percentage of patients (70 per cent) benefited greatly from the treatment and showed excellent symptomatic improvement of cough, dyspnea, pain, and hemoptysis. This improvement lasted, in 50 per cent of the patients, throughout their lives; in 20 per cent of the patients, only a few months; and in the group of patients who lived more than two years, up to two to four months before their deaths.

Complications during treatment were minimal. The skin reaction, after completion of treatment, amounted in the majority of patients to a mild erythema. Fibrosis or telangiectasis in the treated region was not observed one to five years after therapy. Figure 26-11 *top* shows the skin reaction on the anterior chest immediately after completion of supravoltage radiation therapy. A tumor dose of 6,000 r has been delivered through two opposing 15 × 15 cm. fields, bringing a dose of 7,150 r to the skin in a six-week period. We see here just a faint erythema without any moist desquamation. Figure 26-

11 *bottom* shows the absence of any skin reaction one year after completion of therapy that was given with the same factors.

Regarding the final outcome, it is significant that a large percentage (96 patients) died one to twelve months after the completion of radiation therapy (Figure 26-12). Post-mortem examinations revealed generalized metastases in each, which possibly had been present at the time of the beginning of therapy. More significant is the group of forty-eight patients who have lived for more than one year (Figure 26-13). Twenty-four of these patients lived over eighteen months with seven still living; eighteen lived more than twenty-one months; fourteen lived more than two years; ten lived more than twenty-seven months with six still alive; eight more than thirty months with four still alive; seven more than thirty-three months; five more than three years, three of whom are still alive, and four over four years with two still living. One has lived over five years and is in excellent condition. One of the patients who lived four years died in another hospital of a coronary thrombosis, no autopsy was obtained.

Autopsies were performed on twenty patients, who had died one to twenty-six months after radiation therapy. Sixteen showed practically identical findings, consisting of active cancer in the lung associated with radiation changes and widespread generalized metastases. Four autopsies, however, showed complete control of the primary cancer. One patient died of brain metastases one month after completion of therapy. Another patient died of widespread metastases to the opposite lung and many other organs four months after completion of therapy; these were conceivably present at the time radiation therapy was started.

The two other patients did not reveal any metastases at post-mortem examination. Figures 26-14 and 26-15 are photomicrographs of the irradiated lungs, which were described by our pathologist, Edith Sproul, as follows

J McK. Autopsy No. 716 (Figure 26-14). Bronchoscopy biopsy revealed carcinoma differentiated into squamous pattern thought to be bronchogenic.

At autopsy a large, hard mass occupied much

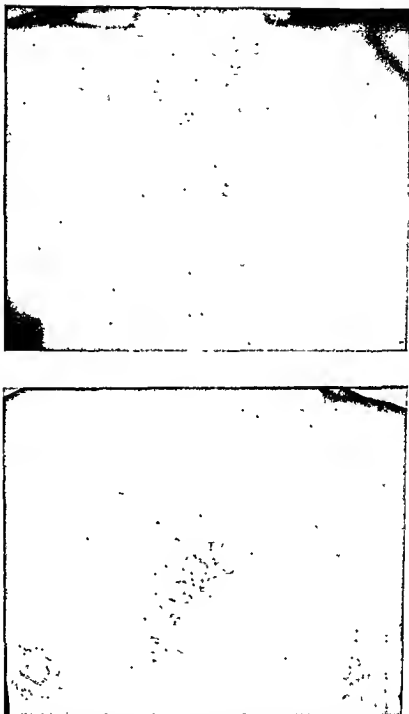


Fig 26-11 (Top) Erythema on anterior chest wall immediately after a skin dose of 7,150 r and a tumor dose of 6,000 r delivered in six weeks' time, utilizing the 2 mev generator. (Bottom) Shows absence of skin reaction one year after a skin dose of 7,150 r and a tumor dose of 6,000 r delivered in six weeks' time. (from R. J. Guttman [1], courtesy Concer.)

26-10B). The histologic diagnosis was carcinoma. The patient received a full course of 2 mev roentgen therapy. A roentgenogram of the chest after completion of treatment showed no significant change (Figure 26-10C). Additional roentgenograms two years

later (Figure 26-10D) and again more than three years later (Figure 26-10E) revealed identical appearances. The patient is a machine operator who is working full time and is asymptomatic.

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Mesothelioma	2
Total	144

SOURCE: R. J. Guttmann [2], courtesy American Journal of Roentgenology, Radium Therapy and Nuclear Medicine.

A high percentage of patients (70 per cent) benefited greatly from the treatment and showed excellent symptomatic improvement of cough, dyspnea, pain, and hemoptysis. This improvement lasted, in 50 per cent of the patients, throughout their lives; in 20 per cent of the patients, only a few months, and in the group of patients who lived more than two years, up to two to four months before their deaths.

Complications during treatment were minimal. The skin reaction, after completion of treatment, amounted in the majority of patients to a mild erythema. Fibrosis or telangiectasis in the treated region was not observed one to five years after therapy. Figure 26-11 *top* shows the skin reaction on the anterior chest immediately after completion of supervoltage radiation therapy. A tumor dose of 6,000 r has been delivered through two opposing 15 × 15 cm fields, bringing a dose of 7,150 r to the skin in a six-week period. We see here just a faint erythema without any moist desquamation. Figure 26-

11 *bottom* shows the absence of any skin reaction one year after completion of therapy that was given with the same factors.

Regarding the final outcome, it is significant that a large percentage (96 patients) died one to twelve months after the completion of radiation therapy (Figure 26-12). Post-mortem examinations revealed generalized metastases in each, which possibly had been present at the time of the beginning of therapy. More significant is the group of forty-eight patients who have lived for more than one year (Figure 26-13). Twenty-four of these patients lived over eighteen months with seven still living; eighteen lived more than twenty-one months; fourteen lived more than two years; ten lived more than twenty-seven months with six still alive; eight more than thirty months with four still alive, seven more than thirty-three months; five more than three years, three of whom are still alive, and four over four years with two still living. One has lived over five years and is in excellent condition. One of the patients who lived four years died in another hospital of a coronary thrombosis; no autopsy was obtained.

Autopsies were performed on twenty patients, who had died one to twenty-six months after radiation therapy. Sixteen showed practically identical findings, consisting of active cancer in the lung associated with radiation changes and widespread generalized metastases. Four autopsies, however, showed complete control of the primary cancer. One patient died of brain metastases one month after completion of therapy. Another patient died of widespread metastases to the opposite lung and many other organs four months after completion of therapy; these were conceivably present at the time radiation therapy was started.

The two other patients did not reveal any metastases at post-mortem examination. Figures 26-14 and 26-15 are photomicrographs of the irradiated lungs, which were described by our pathologist, Edith Sproul, as follows:

J McK Autopsy No. 716 (Figure 26-14). Bronchoscopy biopsy revealed carcinoma differentiated into squamous pattern thought to be bronchogenic.

At autopsy a large, hard mass occupied much

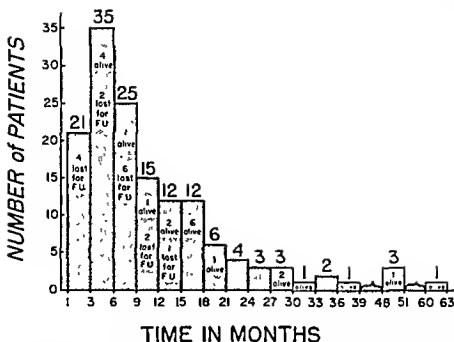


Fig. 26-12. Survival time for 144 patients. (From R. J. Guttman [2], courtesy American Journal of Roentgenology, Radium Therapy and Nuclear Medicine.)

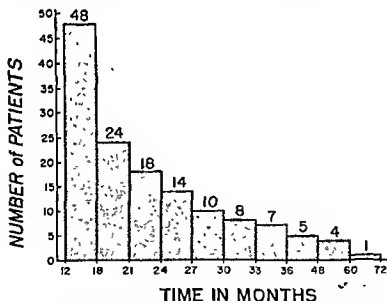


Fig. 26-13. Survival time of forty-eight patients who lived more than one year. (From R. J. Guttman [2], courtesy American Journal of Roentgenology, Radium Therapy and Nuclear Medicine.)

of the right lower lobe. Very many sections from all parts of this, especially about the hilum, showed extensive fibrosis both in the form of complete replacement and as advanced healed interstitial pneumonia. Large distorted multinucleated cells were occasionally found in what remained of shrunken air spaces. These resembled the forms seen following radiation of the were interpreted as radiation effect on cells. No groups or sheets of cells

suggesting carcinoma were found. There were no metastases. The patient has extensive bullous emphysema known to have been present many years. The pulmonary artery to the right lower lobe was thrombosed.

F. E. Autopsy No. 797 (Figure 26-15). Although the bronchoscopic biopsy of the bronchus was only a small fragment it clearly contained undifferentiated sheets of large epithelial cells

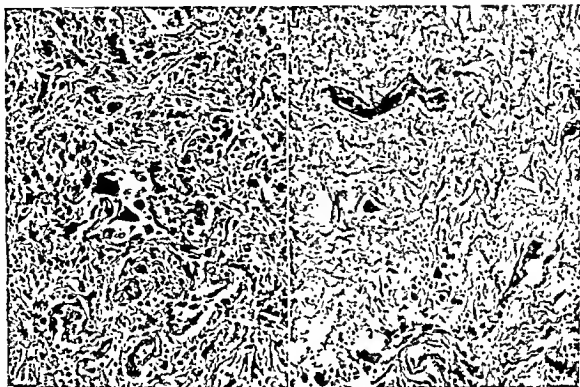


Fig 26-14. Photomicrographs of irradiated lungs. (Left) Fibrosis of lung, showing remnants of alveolar pattern with giant cells thought to be radiation effect on alveolar lining (Right) Fibrosis of lung, more complete (From R. J. Guttman [1], courtesy Cancer)

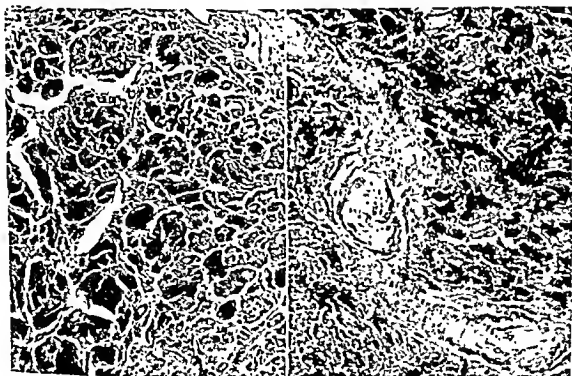


Fig 26-15. Photomicrographs of irradiated lungs. (Left) Fibrosis on wall of bronchus, no tumor. (Right) Silicotic nodule in lymph nodes at hilus of lung. No tumor. (From R. J. Guttman [1], courtesy Cancer.)

thought most likely primary at this site. The area and all the hilar tissues around were extensively sectioned at autopsy. The biopsy site was recognized as showing inflammation and complete fibrosis replacing part of the bronchus and contiguous tissue. Other fibrous areas were clearly old silicotic nodules readily distinguished from the recent hyalinization. Radiation effect on lung parenchyma was slight. No tumor was found in the lung nor were there metastases. The patient was markedly emaciated and had arteriosclerotic heart disease as well as pneumonia.

DISCUSSION

The majority of patients with inoperable lung cancer have been treated with a 2 mev roentgen-ray unit that in our opinion is superior to the cobalt-60 unit for the treatment of pulmonary carcinoma. Most impressive during the treatment were the excellent tolerance that the patients exhibited, the almost regularly displayed symptomatic improvement, and last, but definitely not least, the most gratifying objective success in many patients. Among the observations made in the course of this special study three are of considerable interest. (1) the missing correlation between clinical success and roentgenologic findings, (2) the apparently greater response of malignant lesions of the epithelium compared with those of glandular tissue, and (3) the microscopic proof that it is possible to sterilize even a large carcinoma of the lung with external radiation as previously outlined.

EDITORIAL ADDENDUM

The findings reported by Dr. Guttman reflect reports of other investigators who have used high-energy irradiation in the treatment of inoperable lung cancer.

T. A. Watson, of Saskatchewan, Canada [7], reported on 611 patients. Each of 319 untreated patients died rapidly, only two remaining alive after three years. Of 151 patients who received orthovoltage roentgen therapy, none survived a prolonged period and the survival curve adhered rather closely to that of untreated patients, the only difference being that a larger number of those who received treatment survived the early months. Twenty-eight patients treated with the 23 mev betatron enjoyed a good survival rate during the early months but the survival fell off

precipitously thereafter. (Figure 26-16.) Fourteen patients treated by cobalt-60 teletherapy presented a survival rate similar to that of those treated with the betatron.

Over 75 per cent of the patients treated with high-energy irradiation enjoyed palliation that was considerably superior, in Dr. Watson's estimation, to that offered by orthovoltage irradiation. He concludes: "Supervoltage roentgen therapy seems to offer nothing curative in cancer of the lung. There is, however, evidence of significant palliation. It is suggested that nitrogen mustard combined with supervoltage radiation may be superior to radiation alone."

Hare and associates [2, 3] of the Lahey Clinic and the Massachusetts Institute of Technology reported their experience with twenty-six patients treated with the 2 mev x-ray generator. The dose administered was 175 r per day for 35 treatment days, striving for a tumor dose of 6,000 r. These authors have demonstrated that a dose of 3,000 r is insufficient to destroy pulmonary cancer but that 6,000 r is cancericidal for squamous-cell carcinomas. They reported a study in progress of delivering a cancericidal dose of irradiation preoperatively followed by pneumonectomy.

Harvey has reported excellent palliation with the use of the 22 mev betatron (see Vol. I, Chap. 20). He calls attention to the fact that patients suffering from intractable pain owing to Pancoast tumor enjoyed marked relief from this symptom.

Wheatley, Steed, Savage, King, Forster, Hodt, Jones, and Smithers reported on 25 patients treated at the Royal Marsden Hospital, London, with a 2 mev generator; good palliation was secured. Morrison and Deeley reported on 199 patients with inoperable lung cancer treated with the 8 mev linear accelerator with good palliation but no significant prolongation of survival. Smithers has stated: "In our experience supervoltage irradiation gives symptomatic relief more easily and with far less discomfort to the patient. Improved quality of radiation also gives a better chance to those few patients whose degree of spread has been overestimated or who are technically inoperable but in whom some opportunity for longer survival still remains."

Milford D. Schulz [6] of the Massachusetts General Hospital (Boston), has treated 232 patients with inoperable lung cancer employing supervoltage x-ray therapy—either a 1.2 or 2 mev unit. An average survival of eight months after x-ray therapy was accomplished. About 4 per cent of the patients survived two years; three patients survived more than five years. In contrast, those who received no treatment survived less than three months. He

suffering and anxiety among those with this disease, and for a fortunate few we have been able to secure respite and return to health—in some cases to normal activity—for long periods of time—occasionally for many years.

I can report to you that we are able to offer this to an increasing number of patients and that, with improvement in equipment and techniques and with greater knowledge of the disease, I believe we are doing it more effectively and efficiently and with less harm to the patient carrying the tumor. It remains our object to improve

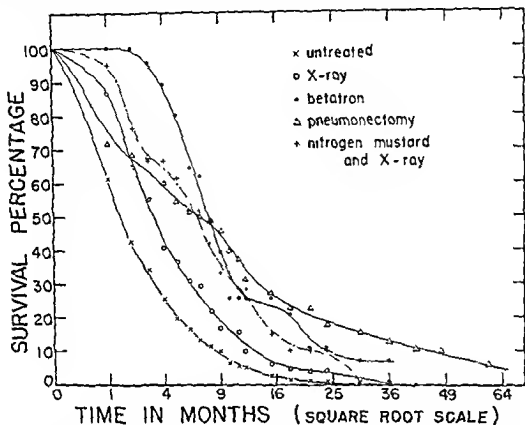


Fig. 26-16 Survival time of patients after various types of treatment (see text). (From T. A. Watson [7], courtesy *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine*)

questions the advisability of administering a radical course of therapy (6,000 r in six weeks or longer) except in selected circumstances.

Schulz summarized his experience as follows:

Finally, I should like to be able to report to you that by radiotherapy we have been able to cure a numerically significant number of cases of cancer of the lung but I can not

I should like to be able to report to you that we are now curing more cancers of the lung than we were formerly; I don't know that at present I can.

I can report to you, however, that by radiotherapy we have been able to relieve a lot of

the potentiality of radiotherapy as a curative agent in this disease, when, for one reason or another surgery—which, as things now stand, I believe still remains the treatment of curable cancer—is not feasible.

In contrast to the above reports, Garland and Sisson [1] do not believe that the palliation of patients with inoperable lung cancer was better with supervoltage than with orthovoltage irradiation.

Clinical experiments are being conducted to note the effects of postoperative irradiation in patients whose neoplasms have been incompletely resected. Guttman has reported on

ten such patients in whom the results were encouraging.

From the data available to date, it would seem that cancericidal doses of radiation can be administered to squamous-cell carcinomas of the lung with the high-energy radiation sources. A few reported post-mortem examinations have demonstrated complete destruction of the neoplasm in the radiation beam. Irradiation can be administered with minimal effect upon the skin, subcutaneous tissue, contiguous pulmonary tissue, and spinal cord and with a minimum of systemic reactions. The nature of the beam from high-energy sources permits of large portals so

that the regional lymph nodes may also be irradiated. Few data are available to indicate whether localized operable neoplasms can be successfully controlled by supervoltage irradiation. To date, high-energy irradiation has not revealed any striking ability to cure patients with pulmonary cancer, and the salvage rate in terms of longevity has not been particularly gratifying. A prolonged course of treatment varying from four to eight weeks, which the patient tolerates well with the exception of daily trips for the treatment, has produced significant but transient palliation in from 50 to 75 per cent of patients so treated.

Treatment of Cancer of the Lung by Interstitial Irradiation

Irving M. Ariel
and
J. Samuel Binkley

"The stump of the pulmonary artery was then ligated separately with catgut and seven radon seeds of 1.5 millicuries each were inserted into various parts of the stump."

This quotation is from the report of Graham and Singer (1933) in which they record the first successful pneumonectomy for can-

parently the first recorded instance of interstitial irradiation for lung cancer performed to control possible residual carcinoma following a pneumonectomy. Since then, efforts have been made to administer a cancericidal dose of radiation, utilizing various radiation sources

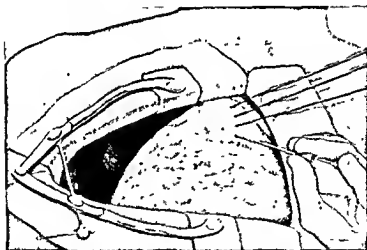


Fig 27-1. Exploratory thoracotomy and implantation of radon seeds under direct visual control. (From J. S. Binkley [4], courtesy *Annals of Western Medicine and Surgery*)

cer. The proximity of the carcinoma to the bifurcation of the main bronchus presumably caused the surgeon to believe that he had not removed all the cancer and to attempt to control any possible residual cancer by means of interstitial irradiation. The patient, a physician, is still actively engaged in the practice of medicine. Evarts Graham tragically died March 4, 1957, of lung cancer. This is ap-

One of us (J. S. B.) first attempted the use of interstitial irradiation in 1939 for tumors found to be inoperable at the time of thoracotomy in two patients with superior sulcus tumors (Figure 27-1). Before these patients were treated, animal experiments had been performed to learn the immediate sequelae to implantation of gold-filtered radon seeds in the lungs of rabbits. The rabbits received

doses ranging from six radon seeds of 0.93 mc. strength to five seeds of 1.7 mc. each. The treated animals showed no ill effects as determined from post-mortem examinations performed from one to six months after treatment. An occasional gold seed migrated into the free pleural space. Several seeds were adjacent to large blood vessels, and one seed was found in the pericardium, without evidence of necrosis. The pulmonary tissue in all the rabbits showed very little radiation fibrosis and central necrosis.

In 1933 Carlson and Ballou [5] had reported their experiences with inserting temporary implants of radium. Several investigators [18, 29] have attempted to insert radon seeds through a bronchoscope into patients with lung cancer for palliation, but obtaining satisfactory dose distribution by this method is most difficult and hence it is not surprising that the results have been discouraging.

In 1949 Ariel, Head, Langston, and Avery [3] reported their experience with seventeen patients having inoperable lung cancer treated with interstitial radon seeds and needles permanently implanted at the time of thoracotomy.

Cliffon, Henschke, and Selby (1958) reported a large series of cases in which the patients were treated with interstitial irradiation, using gold radon seeds, for pulmonary cancers found to be inoperable at the time of thoracotomy, or following partial resection leaving residual cancer. Also in 1958, Henschke [16] reported his experience with 31 patients with inoperable lung cancer treated by permanent implants of iridium 192.

RATIONALE FOR USE OF INTERSTITIAL IRRADIATION

Improved techniques of chest surgery have reduced the mortality rates for thoracotomy to an almost negligible figure. Accordingly, increased numbers of inoperable carcinomas are being discovered at the time of thoracotomy. Inoperability rates have been reported as follows: Churchill (1948), 45 per cent of 1,500 cases; Overholt (1949), 44 per cent of 604 cases; Ariel (1950), 65 per cent of 1,205 cases; Kirklin (1955), 76 per cent of 767 patients.

The results of irradiation administered

through external ports have not been satisfactory. Although palliation can be considerable, increased longevity is seldom obtained and pulmonary fibrosis is a frequent complication. Furthermore, the administration of deep roentgen-ray therapy usually entails a prolonged and somewhat rigorous course of treatment. The average hospital stay for 820 patients treated by roentgen-ray therapy, reported by Ariel and associates, was one and three-tenths months. (See Chap. 18 for a review of the accomplishments and limitations of externally administered irradiation.)

If at the time of thoracotomy a cancer is found to be inoperable or if only a partial resection can be accomplished, rather than close the chest and depend upon external irradiation for palliation it is desirable to take advantage of the exposed neoplasm to apply interstitial irradiation with radioactive sources. The cancer and tumor bed thus exposed offer an ideal situation for interstitial irradiation of the tumor, with protection to the contiguous structures. Furthermore, when only partial resection of the cancer is possible, the residual tumor can be interstitially irradiated. It is also possible to apply interstitial irradiation to intrathoracic lymph nodes that harbor occult or obvious metastases.

Interstitial irradiation offers an opportunity for administering higher tumor doses with minimal damage to normal tissue than does any other available radiologic method. Tumor doses as high as 35,000 rads have been delivered by this technic without complications.

AVAILABLE ISOTOPES FOR INTERSTITIAL IRRADIATION OF PULMONARY NEOPLASMS AND METASTASES

Gold radon seeds and needles, radioactive gold (Au^{198}), radioactive gold coated with silver, radioactive yttrium (Yt^{90}), radioactive chromic phosphate (P^{32}), and radioactive iridium (Ir^{192}) have been used for interstitial irradiation. Other radioactive isotopes, such as radioactive chromium (Cr^{51}), with suitable physical and biologic characteristics, will be developed in the near future for this purpose.

RADON

Gold radon seeds have been the most frequently employed agent for interstitial irradiation.

ation inasmuch as this was the only agent available until recently. Radon has advantages in that it gives off an energetic gamma ray that ranges between 243 and 2,198 kilovolts; the beta rays are absorbed by the gold capsule, and the half life of 3.8 days is satisfactory. A disadvantage of radon lies in the fact that an expensive emanation plant is necessary, which has made it available to only a few

responsible for the infrequency with which lung tumors have been interstitially irradiated.

RADIOACTIVE GOLD (Au^{198})

Radioactive gold has advantages in that it emits an energetic gamma ray of 411 kilovolts and its half life of 2.7 days is satisfactory, and is similar to radon in that a large dose of radiation can be administered in a relatively

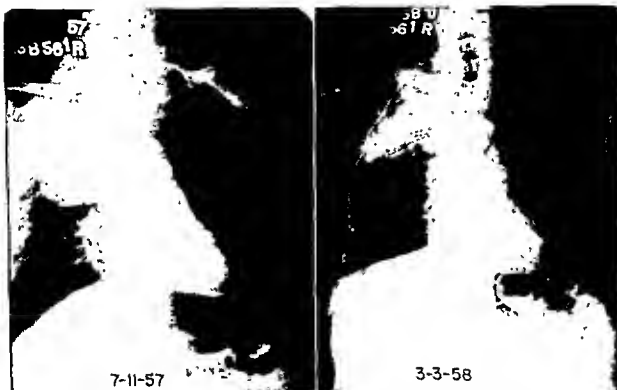


Fig. 27-2. (Left) Roentgenogram illustrating a large oat-cell carcinoma that was found to be inoperable at thoracotomy. The tumor was treated by interstitial irradiation by Dr. Henschke, 284 iridium-192 seeds were inserted, which would produce a tumor dose calculated for total decay of the isotope of 35,000 roentgens. (Right) The appearance of the tumor eight months after the interstitial implant. Note the numerous small iridium seeds within the tumor of the right upper lobe. The patient remains well one year and two months after the interstitial irradiation (Courtesy Dr. Ulrich K. Henschke)

large institutions. Commercially available radon is expensive; 100 mc. would cost approximately \$450 in the United States, and because its use is predicated upon the findings at operation, it would be economically unfeasible to keep a supply constantly in readiness. The diameter of the radon implanter, which measures 1.45 mm. and is equivalent to a 17-gauge needle, makes it somewhat traumatic to insert many trocars of this size into a cancer. An implanter of smaller diameter would be preferable. The disadvantages of using radon have been largely

short period. Its half-value layer in lead, of 2.7 mm., makes it possible to transport it in a relatively small container, in contrast to radon, which has a half-value layer in lead of 7.9 mm. The lower maximum beta energy of Au^{198} (980 kv) in contrast to that of radon (3,170 kv) permits the use of thin shields around the source to filter out the beta rays.

Radioactive gold has been used as seeds, which are inserted through a routine radon trocar (outside diameter 1.45 mm.), and it has also been injected into the tumor as a

colloidal suspension. The material remains *in situ* and is slowly absorbed and transported through the lymphatics, requiring about two weeks for the transport. Accordingly, most of the radiation is dissipated at the site of injection. This technic is similar to the one utilized by Flocks and colleagues for the treatment of cancer of the prostate (see Vol. VII) and by Kottmeier, of Radiumhemmet (Stockholm), for the treatment of cancer of the cervix (see Vol. VI).

RADIOACTIVE YTTRIUM (Y^{90})

Radioactive yttrium is a pure beta emitter, giving off beta rays in a range of 216 kilovolts and having a half life of 2.6 days. It is usually injected as yttrium chloride. It behaves as a colloid and remains at the site of injection, usually producing an yttrium proteinate. The use of radioactive yttrium has been extensively investigated by Joseph Greenberg [10] of the Long Island Jewish Hospital, who has shown that the beta rays of yttrium are highly effective in controlling certain cancers and are not as detrimental as was at one time believed. Furthermore, the narrow penetration path of yttrium offers protection in irradiating cancers that are on the aorta or the heart. This narrow path of penetration is also somewhat of a hindrance in that it requires exact distribution for properly irradiating the entire tumor.

RADIOACTIVE IRIDIUM (Ir^{192})

Radioactive iridium, interstitially applied, has been extensively investigated by Henschke. This isotope emits gamma rays ranging from 136 to 613 kilovolts and has a half life of 74.5 days. When it is administered as a permanent interstitial implant, effective irradiation can be anticipated for approximately 100 days. The long half life permits storage and availability of the isotope. The half-value layer in lead of 2.3 mm. permits transport in relatively small lead containers. The low beta energy of 670 kv permits thin shielding around the source; and the high cross section of iridium (750 barns) to neutron capture makes it possible to produce iridium that has a much smaller diameter than either radon or gold seeds. The iridium seed developed by Henschke has a diameter of

0.3 mm., and can be delivered through a thin needle with an outside diameter of 0.8 mm., equivalent to a 21-gauge needle. Radiation exposure to the operating surgeons during the insertion of the iridium is about one twentieth that of radon or gold. The cost of 100 mc. of iridium is about \$23. The protracted irradiation is beneficial for many tumors.

A disadvantage of iridium is its long half life. The Atomic Energy Commission at the time of this writing has not licensed the clinical application of iridium as a permanent implant because of its reluctance to have patients wandering about with a relatively high dose of radiation present for prolonged periods. Furthermore, an inherent weakness of iridium, as envisioned by the authors, is the fact that a long period must elapse before a cancericidal dose of radiation is administered. This is advantageous for certain slow-growing tumors; but for a rapidly growing cancer it would be preferable to administer radiation over a shorter period.

The present authors have experimented with the use of a short-lived isotope with a high intensity of radiation (Y^{90}) simultaneously with the administration of a longer-lived isotope that emits the radiation more slowly (radioactive chromic phosphate [$Cr P^{32}O_4$] or Ir^{92}).

METHODS OF INTERSTITIAL IRRADIATION OF LUNG CANCER

Ariel, Head, Langston, and Avery [3] reported their experiences with interstitial irradiation of inoperable lung cancer using gold radon seeds and needles. Patients deemed inoperable at the time of thoracotomy because of extension of the neoplasm into the aorta, mediastinum, or other vital structures were treated by interstitial irradiation utilizing three types of gold seeds and needles containing radon. The active lengths were 1, 2, and 4 cm.; the over-all diameter was 0.7 mm. with a 0.3 mm. wall thickness. They contained an average of 1, 2, and 4 mc. of radon, respectively. The plan was to surround the cancer with the large-sized needles and disperse the smaller tubes and seeds throughout the neoplasm, according to the distribution proposed by Qumby. Such accurate distribution was



Fig 27-3. Roentgenogram of a bronchogenic carcinoma of the right upper lobe which was treated by interstitial radon seeds and needles (From I. M. Ariel, J. R. Head, H. T. Langston, and E. E. Avery [3], courtesy Cancer)

difficult, if not impossible, because of the location of the neoplasm in proximity to vital structures (heart, aorta) and the difficulty encountered in differentiating the cancer from the induration of the pneumonitis that often surrounded it. The seeds and needles were introduced by means of the usual radon-seed

inserters and remained permanently. An attempt was made to provide a cancericidal dose to all parts of the neoplasm (Figures 27-3, 27-4, 27-5). Total dosages varying from 3,000 gamma roentgens to 20,000 gamma roentgens were administered.

Henschke has developed a technic for more accurate permanent implantation that he has used successfully for irradiation with gold radon seeds and radioactive iridium (see Vol. I, Chap. 26 B).

Hodt, Sinclair, and Smithers [17] have devised a "gun" by means of which radioactive gold can be "shot" into the tumor; this has been used effectively at the Brompton Hospital in conjunction with the Royal Marsden Hospital (London).

Another method used by the authors has been the instillation of solutions of radioactive yttrium and/or radioactive chromic phosphate throughout the tumor. Radioactive gold can be inserted as tiny seeds (similar to radon) or as a colloidal suspension.

Greenberg has devised a novel method of inserting radioactive yttrium. He incorporates the isotope into linear sources of methyl cellulose. The methyl cellulose dissolves in about 24 hours, leaving a linear residue of the radioactive isotope.



Fig. 27-4 Anteroposterior and lateral views showing the distribution of the radon seeds and needles into the neoplasm shown in Figure 27-3 (From I. M. Ariel, J. R. Head, H. T. Langston, and E. E. Avery [3], courtesy Cancer)

Intrathoracic lymph nodes may be interstitially irradiated by a technic in which solutions of certain radioactive isotopes are instilled within the pleura; these are absorbed and transported via the lymphatics to the regional lymph nodes. Radioactive chromic phosphate ($\text{CrP}^{32}\text{O}_4$) has been used at Memorial Hospital (New York City). A tube is

and delivered to the lymph nodes. Silver colloids are promptly drained into the regional lymph nodes. Inasmuch as it is uneconomical to produce radioactive silver, Hahn has devised a unique technic of coating radioactive gold colloids with nonradioactive silver, which physiologically and chemically behave like silver and have the physical characteristics of

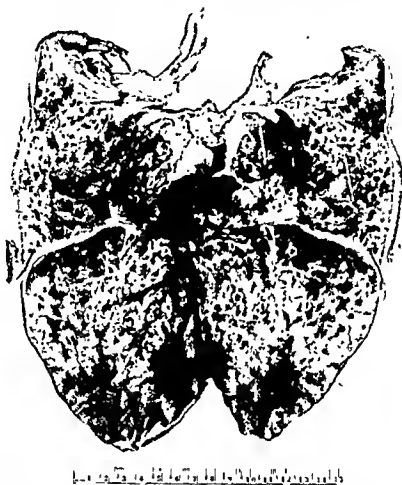


Fig. 27-5. Photograph of a post mortem specimen showing the radon seeds and needles that had been inserted four months previously. A dose of 13,425 millicurie hours had been given. (From I. M. Ariel, J. R. Head, H. T. Langston, and E. E. Avery [3], courtesy Cancer.)

placed into the pleural space at the time of thoracotomy and as soon as all the drains are removed postoperatively, radioactive chromic phosphate is injected into the pleural space. Final evaluation of this procedure awaits establishment. A more desirable isotope is silver-coated radioactive gold, as developed by Hahn.

Hahn has extensively experimented with the use of radioactive gold in the treatment of lung cancer. When gold colloids are instilled into the bronchus, they are slowly absorbed

the gold nucleide. This technic permits an effective method of irradiating metastases to regional lymph nodes. A combination of radioactive gold and radioactive gold covered by silver could be interstitially administered into the cancer and the tumor bed. The naked gold would remain within the tumor, irradiating it; whereas the silver-coated gold would drain to the lymph nodes, producing satisfactory irradiation of metastases. Hahn advocates that, two weeks before thoracotomy, instillation of

silver-coated radioactive gold into an intact nondiseased lobe of the lung on the affected side be undertaken; in two weeks, operation be performed, for at this time the inherent radiation of the isotope would have been largely dissipated; shortly after the operation, especially if a lobectomy or a pneumonectomy can be effected, additional quantities be instilled into the empty hemithorax to provide additional irradiation to the regional lymph nodes. A nationwide program, in which the present

geometry of the neoplasms and their frequent juxtaposition to such vital and vulnerable structures as the heart and the great vessels make it extremely difficult to distribute the radiation source throughout every part of the neoplasm and its metastases.

RESULTS

Seventeen patients reported on by Ariel, Head, Langston, and Avery [3], whose inoperable lung cancers were implanted with



Fig. 27-6 Anteroposterior and lateral views of carcinoma metastatic to the lung from a renal neoplasm, this was injected with 39 mc. of yttrium 90 administered percutaneously. Two cubic centimeters of Lipiodol was included in the injected solution to permit roentgenographic delineation of the injected material. These photographs were taken immediately after the injection.

authors are participating, has been arranged by Dr. Hahn for the instillation of radioactive gold into the hemithorax following resection of pulmonary cancer, in an attempt to learn if a significant salvage can be obtained by postoperative irradiation of occult metastases in regional lymph nodes.

Attempts have been made by one of us (I. M. A.) to inject radioactive yttrium (usually from 10 to 20 mc. of Yt^{90}) into lung tumors percutaneously under radiologic control (Figure 27-6). This technic has been utilized in 15 patients to date, without mishap and with encouraging results.

A truly satisfactory technic for adequately and accurately inserting radiation sources into lung cancers still awaits development. The

gold radon seeds, experienced palliation. The presence of the gold seeds had no deleterious effect upon convalescence. Each enjoyed an essentially uneventful postoperative course entirely comparable to similar but nonirradiated subjects and was discharged on an average of two weeks following the operative procedure. One patient did develop a brisk skin reaction from the interstitial irradiation. In Henschke's series of patients, the median day of discharge from the hospital following thoracotomy and interstitial irradiation was the eleventh day.

Clifton, Henschke, and Selby [7] reported on 108 patients with primary bronchogenic carcinoma found to be inoperable at the time of thoracotomy who received interstitial radon implantation. The operative mortality was 5.6

per cent. The average survival time, including the patients who died postoperatively, was 10.3 months; excluding the operative mortality, it was 10.8 months. The median survival time was 7.0 months. Very little difference in survival was noted when the group was analyzed according to the histologic type of tumor. A slightly improved survival was shown for the group with adenocarcinoma.

PALLIATION

Each of the above-mentioned patients in the series of Ariel and associates enjoyed prompt

malaise, were abated in most instances, and improved appetite with gain in weight occurred.

In one patient the tumor, as visualized by roentgenography, decreased from 6.5 cm. to 3.5 cm. in diameter in one month.

INTERSTITIAL RADON THERAPY IN THE TREATMENT OF THE SUPERIOR SULCUS TUMOR

The poor end results in the clinical management of cancer of the superior sulcus of the lung are well known. The average survival



Fig. 27-7 (Left) Posteroanterior roentgenogram of the chest, showing a right superior sulcus tumor. (Right) Posteroanterior roentgenogram of the chest made fourteen months after interstitial radon therapy, showing regression of the tumor in left illustration. (From J. S. Binkley [4], courtesy *Annals of Western Medicine and Surgery*)

though transient (one to ten months) palliation. In all patients in whom cough had been a troublesome symptom there was a marked diminution in the severity of coughing and in the amount of expectoration.

Chest pains were diminished in all but one patient, in whom the pain was believed due to a rib metastasis. In two patients atelectasis that had been present owing to obstruction of the bronchus by tumor was relieved following the irradiation. The atelectatic lobe in both instances became aerated and the degree of obstruction of the bronchus by tumor, as visualized bronchoscopically, decreased almost to the point of complete patency.

General symptoms, such as fever and

time after the onset of symptoms is about one year, and the patient suffers increasing pain until death. (See Chapter 28 for a discussion of superior pulmonary sulcus tumors.)

A combined method of surgical exposure of the neoplasm and interstitial irradiation was first utilized in 1939 by one of us (J. S. B.). Failure to control pain by external irradiation alone prompted the attempt. The salient features of attempts to palliate patients with the superior sulcus tumor by means of interstitial radon introduced during thoracotomy are illustrated by this patient, a fifty-seven-year-old male opera singer. He suffered a right Horner's syndrome and right shoulder-girdle pain. Roentgenograms of the chest revealed a mass

4 cm. in diameter in the right upper thoracic inlet (Figure 27-7). At thoracotomy an inoperable tumor of the superior sulcus of the right lung, measuring approximately 5 cm. in diameter, was encountered. Aspiration needle biopsy was reported as carcinoma. Twenty-three gold-filtered radon seeds were inserted into the tumor for a total dose of 43.13 mc. The patient's postoperative course was uneventful. One month later his weight was 146 pounds. His Horner's syndrome was improved.

of severe pain, the result of a superior sulcus tumor that had eroded the ribs. An exploratory thoracotomy revealed a firm tumor, approximately 3.5 cm. in diameter, frozen in the thoracic inlet and encroaching upon the subclavian vessels and the nerve roots of the brachial plexus. Aspiration needle biopsy was reported as carcinoma, and twenty gold-filtered radon seeds were inserted into the growth for a total of 24.2 mc. The immediate postoperative condition was good, and the right

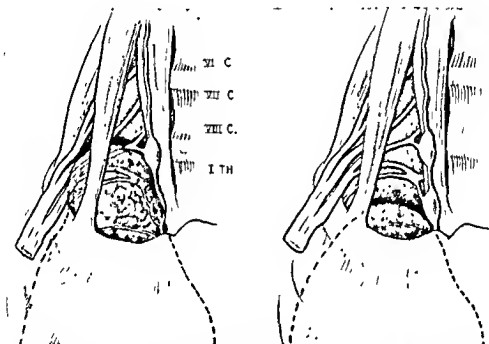


Fig. 27-8. Diagram illustrating regression of superior sulcus tumor, with relief of pain, following interstitial irradiation. (Same case as Figure 27-7). (From J S Binkley [4], courtesy *Annals of Western Medicine and Surgery*.)

He was begun on 1,000 kv supravoltage x-ray therapy; h.v.l. 3.8 mm. Pb, 70 cm. distance, 300 r \times 10, through an 11 cm. circular port anteriorly and posteriorly, for a total of 3,000 r \times 2 or 6,000 r measured in air. Follow-up roentgenograms of the chest showed no further progress of the cancer. Seven months later he developed pain of the right shoulder girdle referred down the right upper extremity, which was in sharp contrast to the seven months' freedom from pain. Another course of x-ray therapy was without effect and the patient succumbed fifteen months after the interstitial irradiation.

Another patient, a morphine addict, was taking 18 grains of morphine a day because

lung re-expanded. His symptoms regressed. Repeat roentgenograms of the chest revealed no evidence of activity of the cancer and he remained in excellent physical condition, with a twelve-pound weight gain. He stopped taking narcotics. Approximately seventeen months after interstitial irradiation his symptoms recurred and he succumbed 29 months post-irradiation.

Of four patients with superior sulcus tumors reported by Hensehke, two have died: one four months and the other thirty-five months after the implantation of gold radon seeds. One patient is living and well over five years after implantation.

INTERSTITIAL IRRADIATION WITH YTTRIUM 90 AND CHROMIC PHOSPHATE (P^{32}) IN INOPERABLE LUNG CANCER

Of fifteen patients treated by the authors whose lung cancers were infiltrated with solutions of radioactive yttrium and/or radioactive chromic phosphate (P^{32}), almost all have enjoyed palliation, sometimes to a surprising degree. Relief of chest pain and diminution of coughing were the major benefits. No significant increase in longevity was noted. The average duration of life was 6.5 months following the interstitial irradiation. No complications occurred in any of the patients treated.

INTERSTITIAL IRRADIATION COMBINED WITH SURGICAL RESECTION

Situations will present themselves wherein it may be possible to resect significant portions of the cancer and implant the residual nonresectable portion. Clifton, Henschke, and Selby [7] report 21 such instances. In nine patients a pneumonectomy was performed, with the prohibitive mortality of 44 per cent. The over-all survival time of this group was 4.7 months; but if those who died as a result of the operation are excluded, the average survival is 8.7 months. In twelve patients a partial resection (lobectomy or wedge resection) was performed, with a mortality of 25 per cent. The average survival time of this group, including those who died at operation, was 17.4 months, and excluding the operative deaths, 22.6 months. Four of these patients are living, from 18 to 100 months.

COMPLICATIONS OF INTERSTITIAL IRRADIATION OF LUNG CANCER

No complications have been observed from the interstitial irradiation of pulmonary can-

cers. One patient reported by Ariel, Head, Langston, and Avery [3], who enjoyed excellent early palliation, succumbed four months following irradiation owing to aggravation of a tuberculous lesion of the opposite lung. The possibility that irradiation contributed to the aggravation of the tuberculous lesion cannot be overlooked.

Henschke reported that a number of his patients suffered from a mild esophagitis believed to be the result of the irradiation. In each case the esophagitis cleared spontaneously.

The difficulty of accurate distribution offers a potential hazard of overlapping of radiation sources, with resultant necrosis owing to overirradiation. If this occurs in the vicinity of a major vessel, hemorrhage may ensue, although this complication has not been observed in any of the reported cases.

ANCILLARY MEASURES

A cancericidal dose of radiation can be administered by the interstitial techniques, and the interstitial irradiation may be supplemented by ancillary measures such as a course of nitrogen mustard or some other chemotherapeutic agent. This has been done in several of our patients, but the results are inconclusive.

If a patient enjoys a good response and at a later date symptoms become bothersome, the patient may be given a second course of irradiation through external ports. External irradiation following interstitial irradiation has been utilized by both Henschke and Ariel and their colleagues, but it is impossible to assess its value except to state that the externally applied radiation was well tolerated, without complications.

Treatment of the Superior Pulmonary Sulcus Tumor

Harold W. Jacox

HISTORIC REVIEW

The study of tumors of the thoracic inlet was stimulated by Pancoast who, in 1924, called attention to a group of apical chest tumors that were associated with pain referred to the shoulder and arm of the affected side and, in addition, with cervical sympathetic phenomena that produced a train of symptoms and findings suggestive of tumor of the spinal cord. He thought that the tumors that gave rise to this peculiar group of symptoms were pleural in origin, but he believed that tumors of the spinal cord, meninges, and neck, as well as cervical rib and vertebral neoplasms, could also produce the same clinical picture. He based his conclusions on a study of four

patients, in three of whom an exploratory procedure was performed, and in two of whom biopsy was done, but in none of whom necropsy was obtained. In 1932 [13] he applied the term "superior pulmonary sulcus tumor" to this symptom complex and enumerated its essential features: (1) homolateral pain around the shoulder and down the arm; (2) atrophy of the muscles of the arm and hand; (3) Horner's syndrome (ptosis, miosis, apparent enophthalmos and anhidrosis); and (4) roentgenographic evidence of a small, homogeneous shadow at the extreme apex of the chest, with a variable amount of destruction of the posterior aspects of the ribs and often adjacent vertebral infiltration. He con-

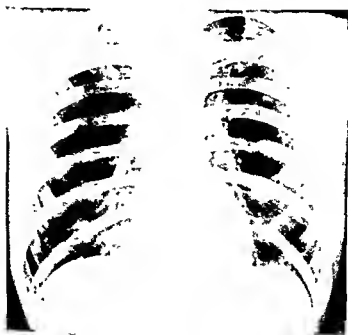


Fig 28-1. Roentgenograph of chest demonstrating growth in the right apex, a typical superior pulmonary sulcus tumor. (From H W Jacox [9], courtesy *Journal of the American Medical Association*.)

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plasm, regardless of its origin, can produce the signs and symptoms mentioned above, titles referring to a particular tumor should be avoided.

Complete necropsies of patients with this syndrome have shown that it is the location of the tumor that is important in producing the symptoms and not its histologic structure. It has been shown that the latter is not uniform but varies from patient to patient and even in the same patient. Because squamous, undifferentiated, and glandular types, some with mucin production, have been found, some pathologists consider a probable origin from bronchial rather than branchial rests. In the majority, the tumor has been secondary to a primary focus, with primary carcinoma of the lung predominating, although many neoplasms have been named as the primary growth. Among these are: carcinoma of the breast, esophagus, stomach, pancreas, larynx, prostate, kidney, and cervix, thymoma, osteogenic sarcoma, supporting-tissue sarcoma, sympathicoblastoma, and Hodgkin's disease. Cases have been recorded in which a careful autopsy disclosed no primary site other than the soft tissues of the neck, confirming Pancoast's original impression that the tumor may arise in an embryonal rest.

INCIDENCE

The condition occurs relatively infrequently and considerable difference of opinion exists as to whether the syndrome can be regarded as a clinical and pathologic entity distinct from primary carcinoma of the bronchus or a pulmonary metastatic tumor. A search of records from January 1, 1928, to December 31, 1937, inclusive, was made at the Mayo Clinic. During this ten-year period only thirteen cases were encountered that fulfilled the criteria described by Pancoast as essential for a diagnosis of superior pulmonary sulcus tumor. Probably more of these tumors will be found in the future because of the increasing incidence of primary lung cancer.

SYMPTOMATOLOGY

As in primary carcinoma of the bronchus, tumor of the superior pulmonary sulcus occurs more frequently in the male than in the female. At no age is one exempt from the neo-

plasm, although the majority of patients are of middle age. The right and left sides seem to be involved about equally.

Pain is by far the earliest and most annoying symptom. It usually begins near the shoulder and spreads down the arm to the elbow and around the scapula. It is usually intermittent in character, worse at night, and often mistaken at first for "rheumatism" or "neuritis." Early roentgenographic changes may be overlooked. Hemoptysis is usually absent, but fixation of a vocal cord may occur early. Surgical exploration usually results in the finding of an inoperable condition because of rib or vertebral involvement.

PATHOLOGY

The term "superior pulmonary sulcus tumor" is not a justifiable term except when used to indicate only that the tumor is limited to a distinct portion of the thorax. The presence of Horner's syndrome is only a manifestation of the degree of spread of an apical tumor. It is related in no way to a specific type of tumor in the thoracic inlet. The tumor that most commonly produces this symptom complex is primary carcinoma of the bronchus or bronchioles.

In most cases, at autopsy it is impossible to separate the entire thickened pleural dome from the lung and it may be that the carcinoma originates in this spot from the terminal bronchioles. The definite and striking syndrome, quite different from that of the usual primary malignant growths of the lung, is a clinical manifestation accounted for by involvement of the nerves and blood vessels by tumor.

PROGNOSIS AND TREATMENT

The prognosis is extremely grave, most patients being dead within a year after their first examination. Up to the present time there does not seem to be any treatment that is successful in dealing with the condition. In an occasional patient temporary relief may be obtained through the use of intensive roentgen therapy, and an effort at palliation with radiation is worthwhile in all patients whose general condition warrants it.

Surgery is unsatisfactory because the nerve plexuses and mediastinum are usually infil-

eluded that it must be considered a distinct new clinical entity caused by a specific tumor arising in an embryonal epithelial rest, possibly derived from the fifth branchial pouch. He said, "The name of superior pulmonary sulcus tumor has been given it because this term implies its approximate location and a lack of origin from lung, pleura, ribs, or mediastinum.

bronchus or sarcoma of a rib. He apparently was unaware of three papers describing cases similar to his, by Hare [7] in 1838, MacDonnell [10] in 1850, and Riealdoni [15] in 1918. Every year since 1932 additional case reports have appeared, some of which attempt to clarify the origin of this neoplasm. The literature contains reports of more than 200 cases



Fig. 28-2. Roentgenogram showing destruction of the posterior half of the right first rib caused by infiltration of a superior pulmonary sulcus tumor. (From H. W. Jacox [9], courtesy *Journal of the American Medical Association*.)

It is possible that this new designation may be changed again with a better knowledge of the histopathology of the growth."

Pancoast's conclusion was based on a review of his four original cases, one of which was discarded, and on four additional cases, in none of which biopsy or necropsy was performed. Owing to the absence of demonstrable metastases and to the absence of one or more of the characteristics he had described, Pancoast dismissed the idea that the condition might be one of primary carcinoma of the

of these tumors having the Pancoast syndrome.

The syndrome has been described under a variety of names: superior pulmonary sulcus syndrome, Pancoast syndrome, apicocostovertebral syndrome, primary carcinoma of the pulmonary apex, sulcus tumor, primary apical lung carcinoma, cancer of the thoracic pulmonary apex, tumor of the superior thoracic inlet, extrapulmonary tumor of the thorax, sternoclavicular branchioma, and others referring to specific tumors. Inasmuch as any neo-

surgery and irradiation. Chardack and MacCallum [2] report the case of a patient with freedom from recurrence or metastases of more than five years following surgical removal of an apical bronchogenic carcinoma producing a Pancoast syndrome and conventional voltage postoperative irradiation. Three weeks after surgery, when pain in the arm and hand returned, a tumor dose of 6,528 r (h.v.l. 2.5 mm. Cu) was delivered in fifty-four days and a successful result was obtained. The postoperative irradiation appears to have been an essential part of the satisfactory control in this instance. The patient died of bronchopneumonia nearly six years after operation and at autopsy no evidence of local tumor or metastases could be found. Dantas also recommends surgical removal of the upper lobe and part of the attached ribs whenever possible, and postoperative radiotherapy.

The question of what is the optimum voltage for the therapy of this condition has not been determined. Equally good palliative results have been obtained with conventional as with supervoltage roentgen therapy.

If pain returns after a full course of roentgen therapy, high cervical chordotomy, multiple posterior nerve root or intercostal nerve sections, or a combination of these procedures should be performed when the general condition of the patient will allow it. Even though the length of life may be only a few months,

the severity of the pain justifies some type of neurosurgical attack. In choosing between chordotomy and multiple nerve root sections it should be remembered that chordotomy must be done above the fourth cervical segment and this carries certain risks, mainly from malfunction of respiratory control. Multiple posterior root section is not a dangerous operation, but if enough roots are not cut relief of pain will be incomplete. It is here that intercostal nerve section may be of great value. Although a completely denervated upper extremity is largely useless, the relief of excruciating pain is worth the handicap. The patient's needs should be anticipated early in the course of the neoplasm while he is able to stand the necessary surgical procedure, before deterioration begins. If the pain is more generalized over the whole upper quarter of the chest and upper extremity, prefrontal lobotomy may be the better procedure.

The only possible way to overcome the difficulties of early diagnosis and give the patient a chance of better palliation is to investigate completely every severe and persistent "neuritis" of brachial plexus distribution, even to the extent of exploratory operation if the cause cannot be found otherwise.

(See Vol. I, Chap. 20, for a discussion of betatron irradiation and Chap. 27 of this volume for a discussion of interstitial irradiation.)

trated. Distortion of the esophagus on a barium x-ray examination and recurrent laryngeal nerve paralysis always mean inoperability. When roentgen findings are definite and a positive biopsy specimen can be obtained from the supraclavicular fossa, cure is out of the question. (See Chap. 18 for additional discussion of the surgical treatment of the superior sulcus tumor.)

If roentgen therapy is used, it should be given with a large tumor dose, cross-firing the shoulder, superior mediastinum, and upper lung field and using bolus material to fill any air space. Temporary palliation of pain can be obtained only after intensive roentgen therapy. This means daily treatment with 200 r (measured in air), half-value layer of 1 to 2 mm. Cu (200 to 250 kv peak, 0.5 to 2.0 mm. Cu), cross-firing the supraclavicular region from front and back through each of two portals measuring 15×15 cm. (Figure 28-3). Each portal should receive between 3,500 and 4,000 r (in air) within a period of 25 to 30 days. With a patient whose shoulder measures 20 cm. in thickness in the mid-clavicular line, 100 per cent of the air dose will be delivered to the center and 130 per cent at a depth of 4 cm. If an air dose of 4,200 r is given to each of two such fields, with slanting convergent portals, the tissue dose in the middle of the fossa will be 4,200 r and the tumor dose 4 cm. deep will be 5,460 r. The central ray is aimed at the center of the supraclavicular fossa and is angled so that the cone is flat against the skin surface as much as possible. Sometimes this is difficult and bolus is used where there is much separation of the cone and skin or where part of the beam is projected into the air.

Radiation therapy is often unsatisfactory because these tumors are particularly malignant and generally refractory to radiation treatment. However, regeneration of rib destruction, as shown by recalcification, has occurred after conventional voltage (200 to 250 kv) and supervoltage (1 million or more) roentgen therapy, and temporary pain relief is sometimes obtained. Haas, Harvey, and Melchor report one patient with rib recalcification and without evidence of cancer thirty-five months after betatron irradiation using eight fields which gave a tumor dose of 11,000

r in twenty-six days. Radiation fibrosis, proved by multiple biopsies, followed this heavy dosage and produced a fluctuating circulatory disturbance. Spinal symptoms after betatron irradiation were found in two of their patients. Smithers [16] reports a similar instance of rib recalcification from betatron treatment, but does not give technical factors or dosage. At the Presbyterian Hospital in New York City, complete rib recalcification followed a tumor dose of 4,250 r of 250 kv radiation in thirty-nine days, but the patient died two years later of extension of the cancer.



Fig. 28-3. Location and size of roentgen portals of entry. The arrow represents the degree of angulation of the central ray (Eye changes of left Horner's syndrome are visible) (From H. W. Jacox [9], courtesy *Journal of the American Medical Association*.)

Of eighteen patients with apical lung tumors treated with radiation by Haas and his associates, one of eight who received conventional x-ray therapy survived eleven years and was regarded as an exceptional curiosity in radiosensitivity. He received a tumor dose of 5,300 r given in sixty days with 400 kv radiation. Of ten patients treated with the betatron, two were living and well fifteen and thirty-one months after irradiation.

Another advance in the treatment of this condition seems to be in a combination of



A



B



C

Fig 29-1. A, Photomicrograph of an alveolar carcinoma in an adult male. B, Gross appearance of the alveolar carcinoma. C, Metastases to the vertebra from the alveolar carcinoma in A and B.

Treatment of Miscellaneous Malignant Tumors of the Lung

Alveolar-Cell Carcinoma, Sarcoma, Hamartoma, and Mesothelioma

Ugo Pinheiro Guimarães

ALVEOLAR-CELL CARCINOMA (PULMONARY ADENOMATOSIS)

INCIDENCE

Bronchiolar or alveolar-cell carcinomas of the lung are relatively rare, fewer than two hundred verified cases having been recorded since its first description, by Malassez, in 1876. At the Mayo Clinic, twelve patients bearing this tumor were observed up to 1951. Also up to 1951, twenty patients with bronchiolar carcinoma were observed among 1,200 patients with lung cancer at the Memorial Hospital (New York). Reviewing the subject in 1955, Decker [18] collected 145 proved cases and added ten more. Earlier (1953), Storey [81] collected 154 cases.

Ikeda (1945), in a statistical study gleaned from the literature, reported the incidence of alveolar-cell carcinoma as 3.9 per cent of lung cancers. Neuberger and Geever [66] placed the incidence at 5 per cent, and Paul (1950) at 20 per cent of lung cancers, which seems an exaggerated estimation.

Another case with necroscopic confirmation is added here (Figure 29-1).

HISTOGENESIS

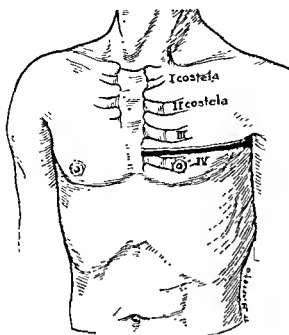
The exact nosology of bronchiolar (alveolar) carcinoma must await precise definition of the histologic nature of the lung alveoli. Meanwhile, the similarity between this neoplasm and jaagsiekte, an infectious pulmonary adenomatosis of sheep, has resulted in efforts to correlate these two entities. The sheep af-

fection is an epizootic pulmonary adenomatosis of global distribution. It tends to be endemic. In the United States it is frequently referred to as "Montana pneumonia." This fatal disease in sheep is known to be infectious by indirect evidence: when healthy sheep are housed with sick animals, they contract the pulmonary affliction. Attempts to isolate the infectious agents and to transmit this ovine malady artificially, either within or outside the specie, have been unsuccessful. Attempts to inject human adenomatosis into animals have also failed to reproduce either a transmissible agent or the neoplasm itself.

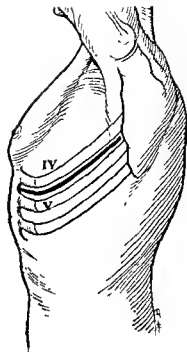
The observation that similar neoplasms can be produced in various animals by different agents, either chemical (1, 2, 5, 6 dibenzanthracene injected subcutaneously into mice, which produced tumors of bronchiolar or alveolar type [Grady]) or bacterial toxins, has led to the belief that nonspecific noxious agents will produce hyperplasia of the bronchiolar (alveolar) constituents that may eventuate in neoplastic formation. These animal data, although intriguing, have not contributed basically to a significant understanding of bronchiolar (alveolar) tumor in the human.

The divergent impressions of the over one hundred authors who have written on the subject during the last few years may be summarized as follows:

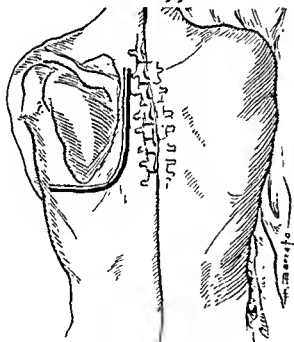
1. Those who admit the existence of alveolar carcinoma originating from the epithelial cells of the alveolar lining.



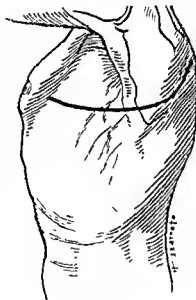
Rienhoff



Lambert



Overholt



*Craaford
Harrington*

Fig. 29-2. Four incisions for thoracotomy.

Examination of Exfoliated Cells

Cytologic studies may diagnose this carcinoma. Papanicolaou has remarked that this tumor exfoliates profusely. Material is obtained in sputum, in aspirated bronchial secretion, and also in pleural fluid. At the Mayo

Clinic, of seven patients in whom a cytologic examination was made, four were positive (three in sputum, one in aspirated bronchial material). Watson and Smith [85] report 80 per cent positive results in fifteen cases; but Decker reports only eighteen positive results in forty-two cases (43 per cent).

2. Those who admit the existence of an alveolar malignant tumor, originating from the mesothelial cells of the alveolar wall, which have differentiated into an epithelioid type.

3. Those who deny the real existence of an alveolar-cell carcinoma as a tumor originating from the alveolar cells, believing that they originate from the basal cells of the bronchial mucosa.

As the presence of epithelial elements in the alveolar wall of the adult is still unproved, here lies the argument for the bronchogenic histogenesis, which I favor. However, the final word is lacking, and morphologic discussions are still presented with the embryologic and histologic comments of the different investigators. There is undoubtedly a more general tendency to classify this tumor as a peculiar variety of bronchogenic carcinoma.

In its relation to the treatment, there remains the question of a unique or a multiple origin of the neoplasm. Here, again, the problem is not entirely solved. Those who profess a multicentric origin could not accept with much sympathy the treatment rigidly based on resectional surgery. Published data, however, indicate that resection provides positive results when—an infrequent possibility—a definite early diagnosis is obtained.

SEX AND AGE DISTRIBUTION

Bronchiolar (alveolar) carcinoma is said to occur more frequently in the female, in contrast to bronchogenic carcinoma. At the Mayo Clinic, seven of the twelve patients were women, whereas at Memorial Hospital only five of the twenty were women. Among the 155 cases reported up to 1955 (Decker [18]), the ratio was three males to two females.

The former impression that this tumor is encountered at an earlier age than the bronchogenic type has not been confirmed. The average age of the patients in the Mayo Clinic and the Memorial Hospital series was around fifty years. In Decker's 155 collected cases, the major incidence was between forty-one and sixty years, more particularly between fifty-one and sixty years.

CLINICAL CHARACTERISTICS

Two types of bronchiolar (alveolar) carcinoma have been described, according to dif-

ferences in the morphology and clinical course: (1) a multinodular type, and (2) a diffuse pneumonic type.

In some instances the morphologic evolution does not show a typical disparity. Herbut [45] reported a case in which one lung contained a nodular tumor coincident with a lesion of the diffuse type present in the opposite lung.

It has been suggested that the diffuse forms might result from the coalescence of individual nodules. Instances of both varieties have been observed in which the clinical course and the morphologic features remained distinct. In Adler's [1] series, fifteen belonged to the multinodular type, four to the diffuse type, and one was a mixed type. Griffith, McDonald, and Clagett [39] found 50 per cent to be the nodular type, 36 per cent diffuse, and 1.4 per cent mixed.

The nodular type is most frequent. All gradations in the size of the nodules are observed, scattered throughout the lung or lungs (Figure 29-1). A bilateral origin seems to be a common feature, being reported by Griffith, McDonald, and Clagett in 69 per cent of their patients.

The diffuse type, with a pneumonic appearance, was first described by Musser in 1903.

DIAGNOSIS

The chances of successful treatment depend entirely upon early diagnosis—a difficult task. In some instances there are no symptoms referable to the respiratory system at the beginning. Moreover, the classic signs and symptoms (cough, sputum, pain, hemoptysis, fever) are not characteristic.

All available diagnostic methods must be employed. Roentgenologic examination, clinical laboratory data, bronchoscopy, cytologic examination of exfoliated cells, and even thoracotomy must all be utilized to diagnose this form of cancer (Figure 29-2).

No typical roentgenologic features are unequivocal proof of bronchiolar (alveolar) carcinoma (Storey and Lawrence [81]). However, the multiplicity of nodules, the location, and the diffuseness of certain lesions suggest the diagnosis.

Inasmuch as there is usually no bronchial involvement, the bronchoscopic picture will not as a rule be informative.

7,272 autopsies. In 1946, Randall and Blades [75] collected from the literature six instances of bronchogenic myoblastoma, two of them malignant, and added one personal observation of a leiomyosarcoma. Ochsner (1948), in a series of thoracotomies in 489 patients with carcinoma of the lung, noted two fibrosarcomas. Black (1949) described a polypoid fibrosarcoma of the bronchus. Overholt observed five sarcomas (exclusive of lymphosarcoma) among seven hundred pulmonary resections, and Graham (personal communication) has observed but one fibrosarcoma (1951). More recently a number of other cases have been reported in the literature. Vernon C. Thompson (1952) added one case; Cecconi [14] seven cases (chondrosarcoma); Galy and Touraine [32] seven more.

Male predominance has been noted in some types. The age incidence varies from childhood to more than seventy years.

DIAGNOSIS

Fibrosarcoma of the polypoid endobronchial type gives symptoms of bronchial dysfunction and obstruction. The diagnosis is made by bronchoscopic examination and biopsy.

The various other locations in the lung of this group of tumors present the usual complexities of progressive symptomatology and, consequently, differential diagnosis is difficult. Cytologic examination may help, and exploratory surgery is frequently necessary.

TREATMENT OF SARCOMA OF THE LUNG

The treatment of sarcoma of the lung is surgical resection.

Bronchoscopic exeresis of an endobronchial fibrosarcoma has been performed, but this cannot be accepted as a reliable procedure. Successful pneumonectomies have been reported by Carswell and Kraeft [13], by Overholt, by Galy and Touraine [32], and by others.

Palliation may be obtained in inoperable cases by irradiation.

LYMPHOSARCOMA

Lymphosarcoma of the lung is usually considered part of a generalized process (lymphoma) and hence is not classified with the

typical pulmonary tumors. However, it does occur as a localized process with sufficient frequency to warrant careful consideration. Included in this group are tumors variously designated in the literature as lymphoblastoma, clasmatocytoma, reticulum-cell sarcoma, and small-cell sarcoma.

INCIDENCE AND CLINICAL FEATURES

Beck and Reganis, in 1951, were able to collect from the literature reports of only six cases of primary lymphosarcoma and added nine cases [5]. A. H. Rose, in 1956, collected 21 published cases that could be considered authentic, and a few have been added since [76].

A tendency to occurrence in young individuals has been noted.

The clinical features of an isolated parenchymal lymphosarcoma of the lung are obscure, and differential diagnosis is difficult in early cases. Later, the presence of fever, pleural effusion, involvement of lymph nodes, and toxemia with anemia may be suggestive.

Cytologic examination of pleural fluid is of diagnostic value. The roentgenographic appearances vary greatly.

TREATMENT OF PULMONARY LYMPHOSARCOMA

Surgical resection is the treatment of choice. Pneumonectomies and lobectomies have been utilized. Churchill, Spatt and Grayzel [80], Ochsner, and Anlyan, Lovingood, and Klasser [3] have reported successful resections. Maier [59] reported a case with 10 5 years postoperative survival. Hazel and Jensik [43] recorded seven operative cases, with four survivals of more than five years (Table 29-1). Two of the patients, treated with partial resection, also had roentgen and nitrogen mustard therapy. Diziembowsky [21] performed decompressive mediastinotomy in two patients suffering from acute mediastinal obstruction; rapid relief of symptoms followed. He states that as a result of the urgent surgical intervention the patient could receive subsequent radiotherapy.

Roentgen or cobalt bomb therapy causes marked shrinkage of pulmonary lymphosarcoma and in some instances may make inoperable tumors operable. It is also used postoperatively and as a palliative measure.

DURATION OF SYMPTOMS

Pulmonary symptoms have averaged less than a year's duration before the patient sought medical attention. In the Memorial Hospital series, the average was 3.8 months. Extensive divergencies are recorded. In nine cases of Decker's collected series, the duration was six weeks. However, there are on record histories of pulmonary symptoms of four years' duration or longer. In a case reported by Delarue and Graham [19], the symptoms were of five years' duration.

METASTASES

According to Neuberger and Geever [66] and others, bronchiolar (alveolar) carcinomas do not metastasize early. Neuberger and Geever report 25 per cent of metastases to bronchial and hilar lymph nodes and 25 per cent to the liver, distant nodes, kidney, brain, and pericardium, in that order of frequency. Griffith, McDonald, and Clagett [39] refer to similarities in the distribution of metastases between bronchogenic and bronchiolar (alveolar) carcinoma; they observed that the adrenals were the site of metastases in 50 per cent of their necropsy series, the brain in 20 per cent, and bones in 20 per cent.

Metastases extend by the lymphatics to the hilar lymph nodes, pleura, and distant lymph nodes; by the blood stream to the liver, kidneys, heart, spleen, etc.; by the aerial (bronchial) route to the opposite lung (Hutchinson [49]). (Figure 29-1).

Available evidence indicates that alveolar-cell carcinomas metastasize with the same rapidity as do bronchogenic carcinomas.

TREATMENT AND PROGNOSIS OF BRONCHIOLAR (ALVEOLAR) CARCINOMA

The fundamental principle of treating bronchogenic carcinoma—i.e., that the only indication, with hope of cure, rests with surgical resection whenever possible—is applicable to this group of neoplasms.

The rapidity of spread of some bronchiolar (alveolar-cell) carcinomas prohibits surgical extirpation. Successful resections have, however, been performed.

Pneumonectomy, lobectomy, and segmental resection have been utilized. Neuhof and Aufses defend lobectomy in selected

cases. At the Mayo Clinic bilateral lobectomy was performed. In Delarue and Graham's patient, who was operated upon with a diagnosis of some inflammatory process, a right lower lobectomy was performed, but the remaining portion of the lung was resected four years later owing to recurrence. Graham thereafter stated that pneumonectomy is safer than a limited operation.

In a group of fifty cases cited by Decker, exploratory operation and biopsy were performed in fourteen patients; pneumonectomy in seventeen; lobectomy in eighteen; lobectomy and lingulectomy in one; segmental resection in four. Of this group, eleven patients were living and well for periods of one to ten years—five for four years, two for five years, one for six years, and one for ten years. Five of these eleven patients were subjected to pneumonectomy and three to lobectomy.

In patients subjected to lobectomy a second resection has sometimes been necessary.

Radical pneumonectomy and pleuropneumonectomy is indicated in patients with hilar lymph node or pleural involvement.

As a palliative measure, ortho roentgeotherapy or irradiation with higher energies (supervoltage irradiation, cobalt teletherapy, or the betatron) may be used in inoperable cases; however, Potts and Davidson (1951) note that bronchiolar (alveolar-cell) carcinoma is a radioresistant tumor.

Chemotherapy with the alkylating agents may offer palliation.

SARCOMA OF THE LUNG

Ewing long ago emphasized the complexities involved in diagnosing and classifying pulmonary sarcomas and described them as "a very ill-defined group of processes of varied origin and course." He made reference to ninety collected instances of lung sarcoma recorded by Adler and stated that only a minority could be accepted.

The following analysis includes fibrosarcoma, leiomyosarcoma, chondrosarcoma, and myosarcoma. Lymphosarcoma and malignant neurilemmoma are discussed separately.

INCIDENCE

Pulmonary sarcomas are indeed rare. Ellis (1939) reported one lung sarcoma among

the lung occur or are discovered more frequently in older individuals.

There may be absence of symptoms, or such pulmonary complaints as cough, chest pain, etc., which are not typical of this entity.

Any of the lobes may be involved, and the tumor may be located either in the hilar or the peripheral region of the lung.

There is nothing characteristic in the roentgenogram except, possibly, small calcifications scattered throughout a discrete, smooth-margined, lobular mass (Hall [41]). In eleven of the seventeen patients reported on by Lemon and Good [52] of the Mayo Clinic, evidence of calcification or ossification was observed.

Bronchoscopic examination is obviously useful in endobronchial localization of the tumor mass.

TREATMENT

The main difficulty lies in establishing a preoperative differential diagnosis and emphasis is therefore focused upon the need for an exploratory thoracotomy. Exeresis of the tumor is generally easily done, resulting in a cure. The endobronchial type of tumor can be bronchoscopically eradicated. Resection can be performed if necessary.

Vascular Hamartoma (Hemangioma)

Blood vessel tumors of the lung vary from simple benign hemangiomas discovered incidentally at autopsy to complex cavernous hemangiomas producing physiologic vascular disturbances as the result of inducing arteriovenous fistula. Such hemangiomas may on occasion be malignant and produce distant metastases.

The diversity of types is responsible for a varied nomenclature: hemangioma, capillary hemangioma, hemangioendothelioma, pulmonary telangiectasis, vascular hamartoma, cavernous hemangioma, arteriovenous aneurysm, arteriovenous fistula.

Lubarsch has called attention to the simultaneous occurrence of multiple foci of hemangioma within the lung. The exact nature of hemangiomas and whether they are or are not true neoplastic formations will not be discussed here (see Vol. VIII); but it should always be borne in mind that some heman-

giomas develop invasive and malignant characteristics.

Attention has lately been focused on the arteriovenous fistulas and reports of new cases have been added to the detailed review of fifty cases by Giampalmo [33]. The frequent hereditary and familial occurrence of arteriovenous fistulas has apparently been confirmed, as has the concomitant occurrence of angiodysplasia of the skin and mucous membrane. Tomography, radiokymography, and angiocardiology are helpful in the identification of arteriovenous fistula.

TREATMENT

Surgical resection is the only reliable treatment for pulmonary hemangiomas. The technics employed vary, depending upon the individual situation, from pneumonectomy (Hepburn and Dauphinee [44]; Goldman [34]), lobectomy (Bisgard, Burchell, and Clagett; Botelho and Fleury da Silva; D'Allaines), segmental resection (Makler and Zion [60], Soulie), excision of the aneurysmal process (Brobeck, Ewing), vascular ligatures (Packard and Waring), ligatures and vascular sections (Watson), to combined operations (O'Neill). Bilateral operations have been performed with success. Owing to the progression of certain cases of arteriovenous fistula, successive operations were performed, with final cure of the patient.

PLEURAL MESOTHELIOMA

Two varieties of pleural mesotheliomas have been described: (1) a diffuse and typically malignant form, and (2) a circumscribed localized form, sometimes of a predominantly fibrous nature. Clagett, McDonald, and Schmidt [16] believe that "Localized fibrous mesothelioma must be sharply distinguished from diffuse malignant mesothelioma."

The nomenclature of the tumor, based on its morphology, is varied: endothelial carcinoma (Wagner), endothelial sarcoma (Podack), primitive pleuroma (Cornil), endoepithelioma (Rabin), pleural endothelioma (Eppinger), mesothelioma (Adami), etc. Krumbein collected thirty different denominations.

Although Lieutaud, in 1776, first described

TABLE 29-1.—RESULTS OF RESECTION IN PULMONARY LYMPHOMA

Patient	Site	Pathology	Treatment	Results
1	L. lung	Hodgkin's sarcoma	Subtotal resection; nitrogen mustard; roentgen	Dead, 8.5 yr. survival
2	R. lung	Small-cell lympho-sarcoma	Right pneumonectomy	Dead; 3.5 yr. survival
3	L. lung	Small-cell lympho-sarcoma	Left upper lobectomy	Lost to follow-up after 2 yrs.
4	R. lung	Small-cell lympho-sarcoma	Right upper lobectomy	Alive 5.5 yrs.
5	R. lung	Lymphoblastoma	Right pneumonectomy	Alive 5.5 yrs.
6	L. lung	Small-cell lympho-sarcoma	Left lower lobectomy	Alive 1.5 yrs.
7	Bilateral	Small-cell lympho-sarcoma	Subtotal resection; nitrogen mustard; roentgen	Alive 13 yrs.

Source: W. V. Hazel and R. Jenik [43], courtesy *Journal of Thoracic Surgery*

Chemotherapy (nitrogen mustard) is of value as supplementary therapy. It is particularly useful as the initial treatment in a patient with distressing and dangerous obstructive or pressure symptoms, because of the rapid response of this tumor to these agents. (See Volume IX for a detailed discussion of the lymphomas.)

NEUROGENIC PULMONARY TUMORS

The histologic varieties of intrathoracic neurogenic neoplasms include neurilemmoma, ganglioneuroma, neurinoma, neurofibroma, and others. They rarely occur primarily in the lungs. (See Chap. 30 for a discussion of mediastinal tumors.)

Tourof and Sapin [83] reported a solitary encapsulated neurofibroma of the lung that occurred in the right lower lobe. Among 196 lobectomies in patients with various diagnoses, Meade, Kay, and Hughes [62] found one instance of a sarcoma of nerve tissue origin. A similar tumor was reported by Diveley and Daniel [20], for which a pneumonectomy was performed, but a recurrence developed and the patient died four months later.

TREATMENT

Surgical resection is the indicated treatment. The type of operation will depend upon the extent and histologic nature of the tumor. Irradiation may be employed postoperatively and for palliation in inoperable cases.

HAMARTOMA OF THE LUNG

Chondromatous Hamartoma

Hamartomas are rare tumors of the lung. McDonald, Harrington, and Clagett of the Mayo Clinic [57] noted twenty patients bearing this entity in a series of 7,972 patients with pulmonary pathology. Novi (1955) collected two hundred cases from the literature; Hodges (1958) stated that about sixty more had been added.

DEFINITION

The term "hamartoma" is derived from the Greek word meaning "to err" and credit is accorded Albrecht [2] who, in 1904, originated this term for an admixture of normal cells grouped together in a tumorlike malformation. Albrecht also utilized the term to describe cavernomas of the liver, spleen, and other organs. The term "hamartoma of the lung" has been used to define a group of tumors in which cartilaginous tissues are a characteristic though not predominant feature. These tumors are more specifically called "chondromatous hamartoma" as distinguished from "vascular hamartoma" (Thompson). According to Bragg and Levene [11], true hamartoma should always be distinguished from pure chondroma, but this point of view is not generally accepted.

CLINICAL FEATURES

There is no proved sexual prevalence. Necropsy findings reveal that hamartomas of

the lung occur or are discovered more frequently in older individuals.

There may be absence of symptoms, or such pulmonary complaints as cough, chest pain, etc., which are not typical of this entity.

Any of the lobes may be involved, and the tumor may be located either in the hilar or the peripheral region of the lung.

There is nothing characteristic in the roentgenogram except, possibly, small calcifications scattered throughout a discrete, smooth-margined, lobular mass (Hall [41]). In eleven of the seventeen patients reported on by Lemon and Good [52] of the Mayo Clinic, evidence of calcification or ossification was observed.

Bronchoscopic examination is obviously useful in endobronchial localization of the tumor mass.

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The nomenclature of the tumor, based on its morphology, is varied: endothelial carcinoma (Wagner), endothelial sarcoma (Podack), primitive pleuroma (Cornil), endoepithelioma (Rabin), pleural endothelioma (Eppinger), mesothelioma (Adami), etc. Krumbein collected thirty different denominations.

Although Lieutaud, in 1776, first described

a tumor originating in the pleura, according to Heuer and Andrus [46] its existence was later refuted by Rokitsky (1843). Notwithstanding, Wagner (1870) recognized its possible primary occurrence and it was he who coined the appellation "endothelkrebs." Moore (1945) commented on the fact that many pathologists still believed the neoplasm to be a secondary tumor. The present tendency is to accept a primary origin, although

Two instances of pleural mesothelioma, both in males, are here added by the author (Figures 29-3 and 29-4).

CLINICAL FEATURES

As previously stated, two varieties of pleural mesothelioma are commonly described: the *diffuse* and the *circumscribed* or *localized*. The former is the more common. In the typical diffuse type, there is marked pleural

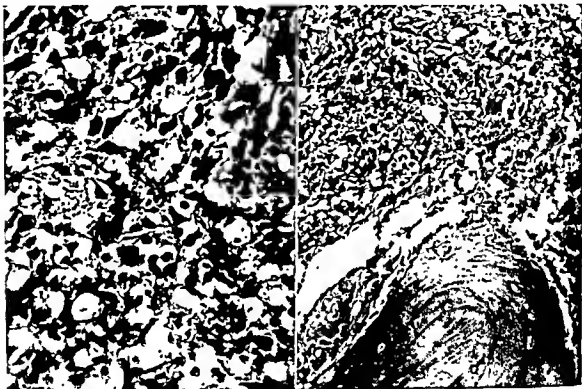


Fig 29-3. Pleural mesothelioma. (Left) Photomicrograph showing polymorphic cells. (Right) Demonstrating invasion of the rib by tumor.

some disagreement persists (Willis [58], Friedmann [31]).

INCIDENCE OF PLEURAL MESOTHELIOMA

Pleural mesothelioma is rather rare. The tumor may arise from the parietal or the visceral pleura. Only four pleural mesotheliomas were encountered in 3,533 necropsies performed at Temple University. Sorenson encountered four cases in 5,800 necropsies. In an extensive review of the literature in 1952, Rubinstein [77] collected 72 cases, in a total of 46,154 necropsies. In 1957, the Brazilian pathologists Tramuja and Artugas [84] reported a case of malignant pleural mesothelioma.

thickening and the pleura appears as a dense white or grayish-white tissue, with multiple nodules and variable degrees of vascularization. The lung is encased. A serofibrinous or hemorrhagic effusion may exist. In the localized type, the tumor may be massive and vascular, and a fibrous type is recognized. Pleural effusion sometimes occurs but is not considered a sign of special malignancy. Invasion of the chest wall was seen in one of our cases.

Chest pain is a dominant symptom in the diffuse type of pleural mesothelioma. The clinical course is variable. Some with very rapid courses have been reported (Bohrod [9]). Heuer and Andrus [46] mentioned a

patient who succumbed two months after the first appearance of symptoms. However, there are clinical histories of one or more years' duration.

In the circumscribed type of mesothelioma, symptoms are also sometimes present for long periods and frequently are extrathoracic.

Metastases, although rare, have been found in the lung, hilar or mediastinal nodes, diaphragm, and peritoneum. Distant metastases have also been described.

TREATMENT OF PLEURAL MESOTHELIOMA

The treatment of pleural mesothelioma of the diffuse type is usually only palliative. Decompressive thoracotomies, with evacuation of the bloody fluid, bring relief of the patient's discomfort.

The type of operation indicated in diffuse tumors, if ever feasible, is pleuropneumonectomy. The parietal pleura is usually adherent to the visceral pleura, at least in some places. The parietal pleura should very carefully be



Fig 29-4. Photomicrographs showing pleural mesothelioma with papillary structure in an adult male (different patient). The patient was treated by pleuropneumonectomy and was symptom-free with no evidence of cancer three years after operation.

DIAGNOSIS OF PLEURAL MESOTHELIOMA

Early diagnosis is usually difficult. The confusion with various pleural lesions is easily understood. Roentgenologic examination in the diffuse type shows only pleural effusion. Draining the effusion may permit visualization of the nodules. Thoracentesis and cytologic examination of the fluid are important diagnostic procedures, although not always positive (Sandi, Rubinstein [77]). Occasionally a diagnostic pneumothorax or pleuroscopy with biopsy is performed. Exploratory thoracotomy is eventually employed in the definitely localized type.

stripped from the thoracic cage by blunt dissection. The subsequent steps of the pleuropneumonectomy technic follow, effecting the removal of the lung and the entire pleural sac.*

In the localized form of mesothelioma there is a possibility of surgical exeresis, as was performed in the two patients here added by the author. One patient, in whom a rib resection was also performed, recovered but did not return for follow-up examination. The other patient was symptom-free with no evidence of

* EDITORIAL NOTE. A technic of pleuropneumonectomy is illustrated in Figure 29-5. This operation has been successfully performed many times.

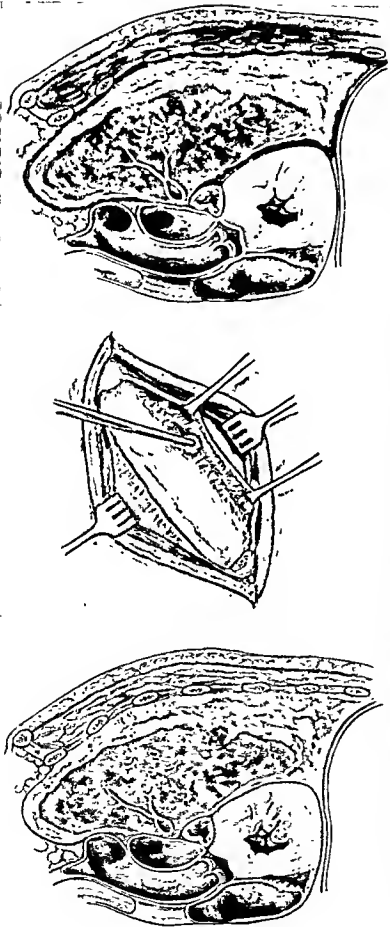


Fig. 29-5. Pleuropneumectomy for pleural mesothelioma. (Left) Sagittal view of pleural mesothelioma which has completely obliterated the pleural space and is intimately adherent to the visceral and parietal pleura. (Center) The incision has been made and a rib resected. The resection commences with dissecting the parietal pleura free from the chest wall. (Right) Sagittal section showing the parietal pleura with the adherent underlying mesothelioma dissected away from the chest wall and the diaphragm. The next step consists of an extrapleural mediastinal dissection and ligation and transection of hilar vessels and bronchus as in the performance of a standard pneumonectomy.

cancer three years after the operation.

In a case of Heuer and Andrus [46], with diaphragmatic invasion, the tumor mass and part of the diaphragm were removed. The patient recovered but the process recurred. Stout and Murray's [82] patient was treated by pneumonectomy and postoperative roentgen therapy for recurrence. He died from metastases twenty-six months after the operation.

Earland [23] maintains that the localized

type of tumor presents a benign evolution and in consequence exceresis of the tumor usually gives excellent results.

Irradiation was used for palliation by Heuer and Andrus [46], Piatt [72], and Meyer, with somewhat varied results.

In pleural effusions, intrapleural nitrogen mustard (20 to 30 mg.) or the intrapleural instillation of radioactive isotopes (radioactive gold, yttrium, or chromic phosphate, P^{32}) may help to control fluid accumulations.

Treatment of Tumors of the Mediastinum

John H. Eckel
and
William DeWitt Andrus

The mediastinum normally contains many different types of tissues. In addition, in the embryologic development of the lungs and heart, the esophagus, and the diaphragm the possibility of misplaced rests is very great. It is therefore not surprising that a wide variety of tumors are encountered in this region.

CLASSIFICATION OF MEDIASTINAL TUMORS

Tumors of the mediastinum may be classified as follows.

- I. Cysts
 1. Dermoid cysts and teratoma
 2. Bronchogenic (ciliated epithelial) cysts
 3. Pericardial cysts
 4. Cysts of endodermal and mesodermal origin
 - a. Gastric cysts, enteric cysts, duplications
 - b. Esophageal cysts, duplications
 5. Cystic hygromas and lymphangiomas
 6. Echinococcus cysts
- II. Connective tissue and neurogenic tumors
 1. Lipoma
 2. Chondroma and chondromyxoma
 3. Xanthoma
 4. Fibroma and fibroleiomyoma
 5. Neurofibroma and neurinoma
 6. Ganglioneuroma
 7. Neuroblastoma and sympatheticoblastoma (sympathicoblastoma)
 8. Neuroepithelioma
 9. Sarcoma of the mediastinum

III. Primary tumors of the mediastinal lymph nodes

1. Lymphosarcoma
2. Hodgkin's disease
3. Endothelioma

IV. Primary tumors of the thymus

V. Carcinoma of the mediastinum

In certain groups, such as lymphosarcoma or Hodgkin's disease, surgery has little or nothing to offer except as a diagnostic aid, but in most of the other mediastinal neoplasms the operative results have become increasingly better.

LOCATION OF TUMORS AND CYSTS OF THE MEDIASTINUM

Schlumberger has listed the location of tumors and cysts of the mediastinum, arranged in the order of incidence and site of relative frequency, in Table 30-1.

SYMPTOMS OF MEDIASTINAL TUMORS

Tumors of the mediastinum, like intracranial neoplasms, give rise to symptoms more or less common to all types. Some tend to indicate the site and to a certain extent the type of tumor present. Among the former are included pain, cough, dyspnea, and cyanosis, while the special symptoms include those of pressure on certain vessels, nerves, or portions of the bronchial tree or esophagus. Thus, the history of Horner's syndrome in a patient with a demonstrable intrathoracic mass strongly suggests the presence of a tumor arising from the paravertebral chain—usually a ganglioneuroma or neurofibroma; and the

TABLE 30-1.—TUMORS AND CYSTS OF MEDIASTINUM IN ORDER OF INCIDENCE AND SITE OF RELATIVE FREQUENCY

<i>Anterior mediastinum</i>	<i>Superior mediastinum</i>	<i>Middle mediastinum</i>	<i>Posterior mediastinum</i>
Thyroma	Goiter	Bronchogenic cyst	Neurilemmoma
Teratoma	Bronchogenic cyst	Lymphomas	Neurofibroma
Goiter	Parathyroid adenoma	Pericardial cyst	Ganglioneuroma
Parathyroid adenoma	Myxoma	Plasma cell myeloma	Sympathicoblastoma
Lymphomas	Lymphomas		Fibrosarcoma
Lipoma			Lymphomas
Fibroma			Goiter
Lymphangioma			Xanthofibroma
Hemangioma			Gastroenteric cyst
Chondroma			Chondroma
Thymic cyst			Myxoma
Rhabdomyosarcoma			Meningocele
			Paraganglioma

Source: H. G. Schlumberger [50], courtesy Armed Forces Institute of Pathology.

expectoration of hair, which occurs on occasion, points to a dermoid cyst, which is commonly found in the anterior or superior portion of the mediastinum.

CYSTS OF THE MEDIASTINUM

Dermoid Cyst and Teratoma

These tumors are congenital and probably arise from rests or misplacements of branchiogenic cells drawn into the thorax by the descent of the diaphragm and heart. They are found most frequently in the superior and anterior mediastinum in front of the great vessels, and often in contact with the pericardium, although they may assume other positions. (Figure 30-1). In a number of the reported cases the tumor apparently arose in connection with the thymus.

Of slow growth, dermoid cysts and teratomas usually remain quiescent for a number of years and may be found incidentally in the course of routine examination. Symptoms often date from an injury or from the onset of other intrathoracic disease. Malignant changes may take place but this is a distinctly rare occurrence.

DIAGNOSIS

X-ray examination is of the greatest value. A spherical, nonpulsating shadow in the anterior or superior mediastinum or projecting out into the lung field from this region makes

the diagnosis almost certain. If bone or teeth are present in the cyst, they may be visible in the x-ray.

TREATMENT

While the advisability of surgery in patients without symptoms may seem debatable, these tumors, if untreated, eventually give rise to serious symptoms, and complications such as infection and subsequent rupture into a bronchus may occur and add to the hazard. The ideal procedure is complete extirpation of the cyst, as this has given the highest percentage of cures and has been associated with the lowest mortality.

The surgical attack on these tumors depends somewhat on their position and size and the presence or absence of infection. In the case of the relatively small cysts located in the anterior mediastinum, an anterior approach through a T-incision (Figure 30-2) will often give adequate exposure, and if the cyst wall is not too adherent to the surrounding structures, may permit its complete removal extrapleurally. For the larger cysts, a transpleural approach through a wide intercostal incision, with rib resections as required for exposure, may be used. Trap-door incisions and longitudinal sternotomy are sometimes suitable procedures.

Cysts located high in the superior mediastinum or tending to project from the superior thoracic aperture may be approached through

a goiter incision combined with high median sternotomy or resection of a portion of the manubrium. The occasional dermoid of the posterior mediastinum may be attacked from behind, often extrapleurally, after resection of the posterior ends of several ribs with or without removal of the corresponding transverse process. In the case of infected tumors,

The bronchogenic cyst is rounded or ovoid, most frequently adjacent and adherent to the carina. Its wall may be thin, fibrous, or cartilaginous, and may contain calcific deposits. It is lined with ciliated columnar or pseudostratified epithelium. Frequently, mucous glands are present. The contents vary from clear liquid to a thick mucoid or viscid mate-



Fig. 30-1. Dermoid cyst of the mediastinum.

it is necessary first to employ adequate antibiotics preoperatively. The more solid teratomas may now be removed in one stage.

Bronchogenic (Ciliated Epithelial) Cysts

Simple cysts with ciliated epithelium have been found in the mediastinum. The etiology is not as yet fully understood, but it has been postulated that they arise as outbuds from the bronchial tree, as diverticula from the trachea, from the esophagus, or from the thymus, which is an endodermal organ.

When these lesions become secondarily infected, the fluid content may be purulent, and rupture into the tracheobronchial tree often ensues.

INCIDENCE

Bronchogenic cysts with ciliated epithelium, although formerly considered rare, are now known to be one of the more common mediastinal tumors. We have observed four patients with ciliated epithelial cysts in a series of 74 cases of mediastinal tumors. Blades, in

1945, reported that 23 bronchogenic cysts had been removed at the various Army thoracic centers over a period of three years during the Second World War. In all, he collected a series of 109 cases of mediastinal tumors operated upon at these centers. That this lesion was encountered so often is of interest, because undoubtedly most patients with chest tumors were eliminated by routine

in 1949 reported a case of bronchogenic cyst in an infant eight months of age, and on surveying the literature collected 82 cases, only three of which were in infants.

CLINICAL FEATURES

Cysts of respiratory epithelium in the mediastinum are generally located near the major bronchi and occur predominantly on

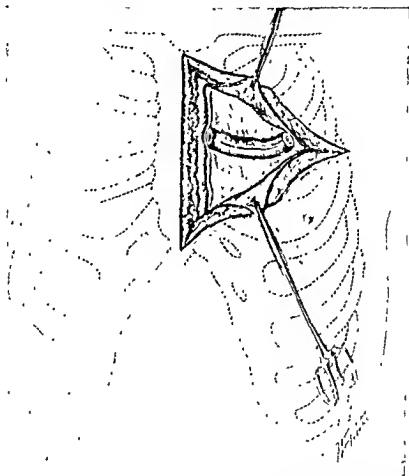


Fig 30-2. Surgical approach to the anterior mediastinum. The height of the approach may be varied by resecting the second and cutting across the first and third costal cartilages. The extent of the exposure may be increased by dividing more than one costal cartilage above and below the resected rib

induction chest surveys. The bronchogenic cyst is often asymptomatic and in many instances is too small for adequate interpretation by the radiologist.

Sabiston and Scott [46] in 1952 surveyed a series of 101 patients with primary neoplasms and cysts of the mediastinum seen during the preceding eighteen years at The Johns Hopkins Hospital and reported only five cases of bronchogenic cysts with ciliated epithelium, four of which occurred in males. Hardy [19]

the right side. The most common site is in the superior mediastinum at the bifurcation of the trachea, with extension between the trachea, vena cava, and esophagus. The cyst may be either anterior or posterior, more commonly the latter. It is rare that there is a lumen connecting the cyst with the trachea or bronchi. In none of the cases collected by Blades was there such a connection.

Many of the cysts reported were discovered at autopsy since, because of their size and

a goiter incision combined with high median sternotomy or resection of a portion of the manubrium. The occasional dermoid of the posterior mediastinum may be attacked from behind, often extrapleurally, after resection of the posterior ends of several ribs with or without removal of the corresponding transverse process. In the case of infected tumors,

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INCIDENCE

Bronchogenic cysts with ciliated epithelium, although formerly considered rare, are now known to be one of the more common mediastinal tumors. We have observed four patients with ciliated epithelial cysts in a series of 74 cases of mediastinal tumors. Blades, in

cations have a two-layered muscular wall resembling the esophagus, and the mucosa may be esophageal, gastric, or a combination of both. There is an intimate attachment to the esophagus. The symptoms caused by this lesion are those of an expanding mediastinal mass as well as those of peptic ulceration. Cough, dyspnea, cyanosis, pneumonitis, dysphagia, regurgitation, hematemesis, and hemoptysis may occur.

Cystic Hygromas and Lymphangiomas

Although cervical cystic hygroma is a well-recognized entity, cervicomediastinal and intrathoracic hygroma without involvement of the neck is uncommon. Gross and Hurwitt [18] in 1948 found only nineteen cases of cervicomediastinal hygroma reported in the literature and added two cases of their own. Sanes, MacManus, and Scatchard [47] were able to find only eight cases of mediastinal cystic hygroma reported to 1945 and added one case; Gross and Hurwitt reported an additional case.

DIAGNOSIS

Mediastinal hygroma is demonstrable by x-ray but cannot be differentiated preoperatively from pericardial, bronchial, or dermoid cysts, teratomas, thymomas, or esophageal duplications. Cervicomediastinal hygromas are readily recognized by the cystic mass in the neck and by the demonstration of the prolonged mediastinal shadow by x-ray. The cervical portion of the hygroma is usually apparent at birth.

TREATMENT

Cystic hygromas confined to the thorax are readily approached by the lateral thoracic incision, as they tend to bulge into either pleural cavity. The cervicomediastinal hygromas are more difficult to excise, and if there are no symptoms of pressure on vital mediastinal structures, the first approach should be cervical as it is frequently possible to remove the intrathoracic portion through the cervical incision. However, if the mediastinal segment is larger and found to be adherent to or enveloping vessels or nerves, a thoracotomy incision must be made.

Because the cystic hygroma, like other cystic

tumors of the mediastinum, is subject to infection and may produce pressure symptoms, thoracotomy and excision of the lesion should be carried out as soon as it is recognized.

Echinococcus Cysts

Echinococcus cysts of the mediastinum (Figure 30-3) are distinctly rare, even as compared with those of the lungs and pleura. The diagnosis rests upon the presence of echinococcus disease elsewhere in the body or the finding of characteristic scolices, hooklets, or part of the cyst membrane in the sputum. Eosinophilia, if present, is suggestive, but is more often equivocal in intrathoracic hydatids than in those of the liver. The Cassoni skin test is also of aid if positive, but the reaction fails to appear in about 10 per cent of the cases.

An interesting group of cases are the echinococcus cysts of the spine, which may have an hour-glass form causing compression symptoms with reference to the spinal cord, and present paravertebral extension into the mediastinum.

TREATMENT

Aspiration of intrathoracic echinococcus cysts is a dangerous procedure. A survey of the reported cases indicates that complete extirpation of the intact cyst or evacuation followed by removal of the cyst wall is the procedure of choice.

CONNECTIVE TISSUE AND NEUROGENIC TUMORS

These tumors of the mediastinum include the pure fibromas, as well as others in which fibrous tissue is only one element in a more or less complex type of tumor containing other tissues of mesodermal origin, as for example the fibroleiomyomas, or of ectodermal derivation, such as the neurofibromas or ganglioneuromas. Chondromas or chondromyxomas are even more frequently encountered, while lipomas and the rarer xanthomas also occur in this region.

Lipoma

Approximately forty-five cases of lipoma involving the mediastinum have been reported in the literature. These may be conveniently

location, they cause no symptoms. Others, owing to their origin close to the air passages, produce symptoms of pressure on these structures or on the esophagus or great vessels.

DIAGNOSIS

Establishing the diagnosis is not always possible before operation. Differentiation from the more common dermoid cyst is sometimes suggested when the x-ray shows a rounded mass just above the hilus intimately associated with the tracheobronchial tree, most frequently at the carina. On fluoroscopy, bronchogenic cysts frequently move with deglutition, whereas pericardial cysts move with the cardiac pulsation. Angiocardiography, kymography, and laminagraphy help to exclude aortic aneurysm and intrapulmonary lesions.

TREATMENT

Although some of these cysts cause no symptoms, operation is advisable because many tend to increase in size and thereby compress the surrounding mediastinal and pulmonary structures, and some ultimately become infected, with serious consequences. The procedure of choice is total excision. Antibiotics should be started preoperatively if there is evidence of infection.

Pericardial Cysts

Pericardial cysts are thin-walled, lined with mesothelium, contain clear fluid, and are usually unilocular. They are most commonly found in the cardiophrenic angle adjacent to the pericardium, the diaphragm, and the anterior chest wall. There is no firm attachment to surrounding structures. They are readily demonstrable on chest x-ray as round or oval outlines of uniform density. On fluoroscopy, the contour may change on respiration, and not infrequently they are seen to move with the cardiac pulsation.

The treatment is total excision.

Cysts of Endodermal and Mesodermal Origin

These tumors would appear to have arisen from cells displaced during the development of the upper gastrointestinal tract, lungs, and

bronchi, and have thus come to contain such tissues as ciliated epithelium, mucous glands, cartilage, or gastric mucosa. They are usually thin-walled and contain clear, milky, or opalescent and rather viscid fluid. Differentiation from the dermoid cysts has not been possible before operation or aspiration, and, indeed, the distinction rests on histologic rather than on clinical grounds.

They may be treated by extirpation.

GASTRIC AND ENTERIC CYSTS AND DUPLICATIONS

These cysts characteristically have linings similar to that of any portion of the gastrointestinal tract, and are situated in the posterior mediastinum at the root of the lungs. They are adherent to mediastinal structures and the lungs, and may be adherent to or even extend below the diaphragm. Davis and Salkio [11] in 1947 found twenty-five cases of gastric cyst reported in the literature; of these, eighteen had only gastric mucosa, while seven had gastric and esophageal mucosa. Eighteen of the cases presented on the right side. Symptoms—commonly dyspnea, cyanosis, cough, hematemesis, hemoptysis, dysphagia, and regurgitation—may be severe and are due to pressure on mediastinal structures or to ulceration of the mucosa.

Davis and Barnes [12] reported a case of intrathoracic duplication of the jejunum. The patient, a five-year-old female child, was admitted to the New York Hospital on several occasions because of tarry stools. At operation a large intrathoracic duplication was found to extend from the proximal jejunum through the diaphragm to occupy the posterior mediastinum. The duplication was removed through both a thoracic and an abdominal incision. In surveying the literature, these authors found that six other cases of this condition of the alimentary tract communicating with the small intestine had been reported up to 1952.

ESOPHAGEAL CYSTS AND DUPLICATIONS

Esophageal duplications are cystic structures of variable size with thick walls and a membranous lining. They arise in the posterior mediastinum and expand into the right or left hemithorax. Histologically the dupli-

Chondroma, Chondromyxoma, Chondromyxosarcoma

It is necessary to use these names in designating these tumors for they usually contain myxomatous as well as chondromatous elements, and are very likely to undergo malignant change. Such tumors, most frequently arising from the costal cartilages and adjacent ribs, may also originate in the sternum or from the vertebral column and project into the mediastinum. More common in adults than in children, they usually appear as circumscribed, sharply demarcated, and often nodular tumors and are not invasive unless malignant. In size they may reach the dimensions of a child's head, and their consistency depends upon whether the chief component is cartilage or the softer or even semifluid myxomatous tissue. Metastases in the lungs may develop in the later stages of the malignant tumor.

DIAGNOSIS

These tumors are of slow growth and pain is an early and often the only symptom. The location, type, and severity of the pain vary with the site of the tumor. When the growth arises from the costal cartilages or ribs, an external mass may be noted by the patient, sometimes before any pain or other symptom. Cough and dyspnea are rarer and later symptoms, but may increase in severity as the tumor grows. With the large tumors, evidences of mediastinal pressure such as suffusion of the face, cyanosis and vascular engorgement, hoarseness, dysphagia, or the signs of pressure on the sympathetic chain may be present. The roentgenogram shows a circumscribed and often nodular shadow, and the site of origin can sometimes be demonstrated.

TREATMENT

Surgical removal usually gives satisfactory results. This is particularly true when operation is undertaken before the tumor has grown too large. Complete extirpation of these tumors requires en bloc removal of entire sections of the chest wall, including the parietal pleura and sometimes even portions of the lung and diaphragm. Whenever possible, the incision should be so planned as to

furnish a musculocutaneous flap that will be of aid in closing the defect. Paralysis of a hemidiaphragm, by interrupting the phrenic fibers, is rarely indicated in attacking mediastinal neoplasms.

Xanthoma

It appears that only a very few cases of mediastinal tumor diagnosed as xanthoma on pathologic examination have been reported. These are benign tumors and amenable to operative removal. In one of the reported cases pleural effusion was present.

Fibroma

Pure fibromas are rare in the mediastinum, most of the reported tumors containing other connective tissue elements as well. They are often adherent to the mediastinal structures or to the pleura or diaphragm, are well encapsulated and, like fibromas elsewhere, are of variable consistency. The symptoms and signs are those common to other tumors of the region. Positive diagnosis has been possible only at operation or autopsy.

TREATMENT

Surgical resection is indicated if possible, since in a group of eighteen reported patients thirteen died who were not operated upon, while all the five subjected to surgical excisions recovered.

Neurogenic Tumors of the Mediastinum

In our series of seventy-four patients with primary mediastinal tumors treated at the New York Hospital, twenty-three of the tumors were neurogenic in origin: of these, seventeen were benign and six were malignant. The seventeen benign tumors were classified as follows: five ganglioneuromas, six neurilemmomas, five neurofibromas, and one neurogenic tumor of undetermined type. Treatment consisted of total excision in twelve cases. There were no complications and there was no mortality. The six malignant tumors were classified as follows: three neuroblastomas, one neurogenic fibrosarcoma; one neuroxanthoma, one glioblastoma multiforme. Three of these were hourglass tumors.

Blades reported twenty-nine cases of benign neurogenic tumors of the mediastinum, in-

divided into three groups: (1) a group, comprising about two thirds of the total number, in which the tumor is entirely intrathoracic; (2) a group in which the tumor is roughly dumbbell in shape, the intrathoracic and extrathoracic portions being connected by a narrow isthmus that traverses an aperture in

cated outline and with its central portion denser than the periphery should make one consider lipoma as a possible diagnosis. When such a shadow is present within the thorax beneath an external tumor in the chest wall or neck, with the physical findings of a lipoma, the diagnosis is suggested.



Fig. 30-3. Echinococcus cyst of the mediastinum.

the thoracic wall; (3) a group in which a mediastinal tumor extends upward into the neck.

Because of their slow growth and soft consistency, these tumors are often slow to produce pressure symptoms and they may grow to considerable size, in one case (Leopold's) weighing 17.5 pounds.

DIAGNOSIS

The diagnosis of intrathoracic lipoma has seldom been made before operation or necropsy, but the presence in the roentgenogram of an intrathoracic shadow of clearly demar-

TREATMENT

Extirpation of these tumors, regardless of their size, should be carried out.

In a series of twenty-five cases reported in the literature, the outcome was as follows: of twelve patients in whom the tumor was only partly intrathoracic (an external tumor was also present), eleven were operated upon and one died untreated; seven of the eleven were cured, while four died. The tumor was entirely intrathoracic in thirteen and ten of these died untreated, while the three in whom the tumor was removed were cured.

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Blades reported twenty-nine cases of benign neurogenic tumors of the mediastinum, in-

cluding ganglioneuromas, neurofibromas, sympathicoblastomas, that were removed successfully at Army Thoracic Surgery Centers in the United States during a three-year period.

Neoplasms of neurogenic origin are the most common posterior mediastinal tumors. In 1944, Kent, Blades, Valle, and Graham [31] collected 105 instances from the litera-

ture and added thirty-three cases seen at the Barnes Hospital between 1944 and 1950. Godwin, Watson, Pool, Cahan, and Nardiello [16] in 1950 reported on twenty-four additional cases from the pathology laboratories and the Thoracic Surgical Service of Memorial Hospital (New York). It is apparent that neurogenic tumors of the mediastinum are common.

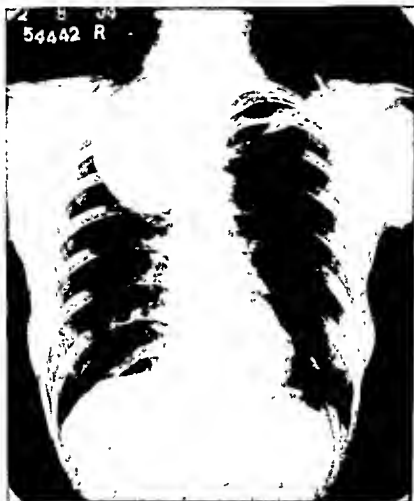


Fig. 30-4. Myxoneurofibroma of the mediastinum

ture and reported twenty-one additional cases of neurogenic tumors from the Barnes Hospital. They noted that 37 per cent of the reported primary nerve tumors had undergone malignant changes. It is therefore apparent that surgical excision should be carried out as soon as the growth is recognized. Roentgen therapy is without benefit in both benign and malignant mediastinal tumors of neurogenic origin. Since Kent's series, Ackerman has found an additional fifty-six cases reported in

NEUROFIBROMA, NEURINOMA, NEURILEMMOMA

Arising from the sheaths of the thoracic nerves or the paravertebral sympathetic chain, these tumors are usually found in the posterior mediastinum. (Figure 30-4). The clinical features are similar to those of ordinary fibroma, but pain, tending to radiate along the course of the intercostal nerves, is an early and prominent symptom. Composed of fibrous tissue and cells derived from the neurilemma, they

may also contain nerve fibers as well as some of the more primitive connective tissue elements such as myxomatous tissue. When such tumors arise in the intervertebral foramina, they may extend into the spinal canal as well as into the thorax, giving rise to hourglass tumors, and often causing symptoms of compression of the spinal cord. Laminectomy as well as thoracotomy may be required for their removal.

In the case of neurofibromas of the intercostal nerves, some erosion of the ribs immediately above and below the site of origin of the tumor may be evident in the x-ray picture, which otherwise simulates closely that of ordinary fibroma.

The treatment is surgical excision and the prognosis is good, provided operation is undertaken before the tumor has attained great size or has undergone malignant changes.

GANGLIONEUROMA

More than one hundred such tumors have been reported, and we have had five in our series. They are being recognized more often in children. Grossly they appear as firm, lobulated tumors of varying size, up to 10 cm. in diameter. Microscopically they are composed of a reticular network containing numerous multipolar ganglion cells.

The symptoms are those of intrathoracic fibromas, but when Horner's syndrome appears early or is the initial symptom, a ganglioneuroma should always be suspected.

These tumors can be removed surgically, which is the only treatment for this neoplasm.

NEUROBLASTOMA (SYMPATHICOBLASTOMA)

More rarely found in the mediastinum are the neuroblastomas or sympathicoblastomas, tumors whose cells represent the primitive states in the development of the sympathetic nervous system. Like the other neurogenic tumors, they may assume an hourglass shape, growing into the spinal canal as well as into the mediastinum.

NEUROEPITHELIOMA

One instance of this rare tumor composed of primitive spongioblasts has been reported

as occurring in the mediastinum. The patient, a woman twenty-three years of age, was operated upon by Sauerbruch and the tumor successfully removed.

TREATMENT OF NEUROGENIC TUMORS OF THE MEDIASTINUM

The treatment of mediastinal tumors of neurogenic origin is surgical removal. The

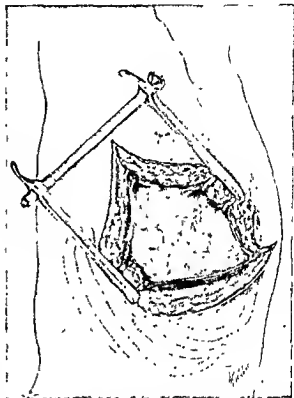


Fig 30-5. Transpleural approach to large mediastinal tumors. This approach may be used with or without resection of a considerable portion of one rib, and the exposure increased by dividing the costal cartilage or posterior ends of the ribs above and below the incision. The height of the exposure can be varied with the rib or intercostal space chosen.

transpleural approach gives the best exposure in removing tumors of this type (Figure 30-5).

Sarcomas of the Mediastinum

Under this heading are grouped those cases of malignant connective tissue tumors that include such types as fibrosarcoma, liposarcoma, myxosarcoma, etc. Whereas in some the process begins as a true sarcoma, in many it is the result of malignant degeneration of a benign tumor, and this fact must be borne in mind in

considering the treatment of apparently benign mediastinal neoplasms.

PRIMARY TUMORS OF THE MEDIASTINAL LYMPH NODES

The mediastinal lymph nodes may be the site of several varieties of primary neoplasms. Those most important from the surgical standpoint are lymphosarcoma, Hodgkin's disease, and endothelioma of the lymph nodes. Surgery has little to offer in these conditions, but a knowledge of their diagnostic features is of great importance with regard to differential diagnosis. Interstitial irradiation applied at the time of thoracotomy is of great value in treating these lymphomatous masses, and bounding the mass with silver clips outlines the target for externally administered irradiation. (See Vol. IX for a discussion of the lymphomas.)

Lymphosarcoma

This is the most common type of neoplasm encountered in the mediastinum, constituting as high as 50 per cent of some series. It occurs most frequently between the ages of thirty and fifty years and predominantly in males (two to one). Because the condition may arise in the thorax and extend to the nodes of the neck, or vice versa, enlargement of the cervical nodes is often evident. Cough is usually dry or frothy expectoration, but hemoptysis is not uncommon. Low-grade fever, below 100° F., is the rule even in the absence of complications.

DIAGNOSIS

The roentgenogram shows an irregular widening of the mediastinal shadow, particularly in its supraaortic portion. Lymphosarcomas of this region are usually sensitive to irradiation, and the decrease in size noted after controlled dosage of x-rays may be very useful in differentiating them from the relatively more radioresistant benign tumors, endotheliomas, and carcinomas.

TREATMENT

Irradiation is the treatment of choice, and great relief of symptoms may follow temporarily but recrudescence appears and the effectiveness of irradiation diminishes with

successive treatments. The use of the nitrogen mustards in such patients may give relief.

Hodgkin's Disease

This disease must be considered with mediastinal tumors from the standpoint of differential diagnosis since it often causes similar symptoms. While certain prodromal symptoms such as itching or eczematous eruptions may be present, enlargement of the lymph nodes constitutes the initial symptom in 50 to 80 per cent of the patients (Figures 30-6 and 30-7). Beginning most commonly in the cervical nodes, the disease may spread to involve those of the mediastinum or, more rarely, the mediastinal nodes may be the primary site. The enlarged mediastinal nodes may remain discrete or they may fuse into a more or less solid mass encircling the great vessels or the air passages. The superior vena caval syndrome of obstruction occasionally occurs. The lungs, pleura, pericardium, cardiac muscles, or liver may be secondarily invaded.

DIAGNOSIS

On the basis of symptoms and physical signs alone, Hodgkin's disease cannot be distinguished from lymphosarcoma, and the diagnosis rests largely on histologic examination of excised tissue, and even then differentiation may be extremely difficult. Differentiation is not entirely necessary as both are usually radiosensitive to a certain degree. In both, however, recurrence commonly follows, and while life may be prolonged, cures are seldom obtained.

Endothelioma

Endothelioma primary in the mediastinal nodes is rare, these nodes being more often involved in the spread of pleural endothelioma. Differential diagnosis can be made only on microscopic examination.

PRIMARY TUMORS OF THE THYMUS

Benign tumors such as cysts, cystic lymphangiomas, lipomas, and the very rare congenital myxoma may occur in the thymus, but many of the reported primary thymic tumors have been malignant (see Chap. 31).

Fig. 30-6 Hodgkin's disease before irradiation.



Fig. 30-7. Hodgkin's disease after irradiation.

CARCINOMA OF THE MEDIASTINUM

Under this heading is included a rather heterogeneous group of primary and secondary malignant tumors. Some of the former may arise from unrecognized dermoids or from the reticulum of the thymus, but in others the origin is uncertain. The secondary tumors result from extension of bronchogenic carcinomas or from metastases from malignant tumors of the breast, esophagus, or more distant organs. In the case of cancer primary in the mediastinum or extending into this region from primary carcinomas in the im-

mediate vicinity, signs and symptoms of compression of the mediastinal organs are more likely to occur than is the case with metastases from a distant focus, as in the latter instance the lungs and other structures are commonly so extensively involved that the patient succumbs before the mediastinal metastases reach large proportions.

In the absence of a recognizable primary carcinoma elsewhere or of superficial nodes that can be excised for study, the diagnosis can only be made after exploration or at autopsy.

Treatment of Tumors of the Thymus

O. Theron Clagett

and

John R. McDonald

The thymus in man develops from the third branchial clefts on both sides; the two outgrowths come into contact in the mid-line in front of the trachea and the organ descends into the thorax to spread out as a bilobed gland over the upper part of the pericardium. The thymus consists of lobules bound together by connective tissue, made up of an outer cortex of closely packed thymocytes or lymphocytes and a medulla consisting of large epithelial cells. Hassall's corpuscles are found in the medulla of the normal thymus and consist of a hyaline center surrounded by layers of flattened cells with poorly staining nuclei. Hammar has expressed the belief that the thymus is an ectodermal structure that later is invaded by lymphocytes derived from the mesoderm. Certainly the small "thymic" cells are indistinguishable histologically from lymphocytes. The thymus continues to enlarge until the age of puberty, then gradually becomes smaller and atrophic but never entirely disappears. Although the embryologic origin of the thymus in association with the thyroid gland, its epithelial cell elements, and the changes it undergoes during growth and development and in association with some diseases (such as hyperthyroidism and Addison's disease) suggests that the thymus should belong to the endocrine system, it has never been proved that it has any purpose or function. The gland can be removed from the experimental animal without detectable alteration in growth, development, or function.

The thymus gland was so named by Galen in the second century A.D., because of its

likeness to a bunch of thymic flowers. From the time of Galen to the present, the thymus has remained an enigma. An editorial has described the situation very well when in a discussion of this organ it was stated, "Endocrinologists have wooed it in vain. Physiologists and pathologists have drawn away from it baffled. Not even the anatomists or the histologists have spoken of it with their customary precision, for we are still uncertain whether it has any real existence in the normal adult, and whether the main cells of its medulla are to be regarded as epithelial or endothelial" [5].

CLASSIFICATION OF THYMIC TUMORS

Tumors of the thymus have presented as much of an enigma as the normal gland itself, as evidenced by Ewing's statement in 1916 that "no group of tumors has more successfully resisted attempts at interpretation and classification than those of the thymus." Among the names applied to these tumors are thymoma, malignant thymoma, thymic epithelioma, carcinoma, perithelioma, lymphosarcoma, thymoma (lymphosarcoma type), and benign lymphocytic thymoma.

A thymoma is defined as a slowly growing tumor of the thymus that has arisen from both the epithelial (reticulum) and thymocytic elements of the thymic parenchyma. Typical Hassall's corpuscles are absent in most thymomas. Features common to thymomas are a dense fibrous capsule; distinct fibrous trabeculae; the palisading of epithelial cells about cystic spaces, about blood vessels, and

about fibrous trabeculations; foci of necrosis or cyst formation and of calcification; but a number of tumors lack one or more of these features. All, however, contain the thymic lymphocyte or thymocyte and the thymic epithelial cell in varying proportions.

The association of thymic tumors with myasthenia gravis has been confirmed by many observers since it was first reported by Weigert in 1901. In our series of three hundred cases of myasthenia gravis observed since 1941, thymic tumors occurred in 15 per cent. In a group of forty-five thymic tumors observed, myasthenia gravis was present in thirty-four, or 75.6 per cent. It is impossible to dismiss this frequent association of a rare tumor with a relatively rare disease as simple coincidence. It is generally agreed that changes in the thymus gland are the most conspicuous and constant anatomic changes in the patient with myasthenia gravis. Nevertheless, all efforts to prove this association beyond doubt or to influence the course of myasthenia gravis by removal of a thymic tumor or a thymus without tumor have failed. Our experience indicates that in those cases in which myasthenia gravis and thymic tumors coexist there is no definite relationship between the appearance of the thymic tumor and the development of symptoms of myasthenia gravis. In some cases a thymic tumor was present for several years before the development of myasthenia gravis; in others the thymic tumor apparently appeared long after myasthenia gravis had developed. All efforts to extract a curare-like substance from thymic tumors have failed. Even though we remain convinced that there is some obscure connection between the thymus and myasthenia gravis, it must be admitted for the present at least that a direct causal relationship is highly unlikely.

Much of the confusion that has existed regarding the classification of thymic tumors has resulted from the inclusion, by a number of authors, of tumors that were not primary in the thymus, such as small-cell carcinoma of the lung with extensive mediastinal involvement, malignant teratomas of the mediastinum, and lymphomas. It must be recognized that the thymus is made up of two types of cells: epithelial cells and thymocytes

or lymphocytes. Tumors of the thymus contain both elements but the relative proportion of these cells varies greatly from tumor to tumor and often from place to place in the same tumor. Tumors in which the epithelial cells predominate are likely to be diagnosed as carcinomas or epitheliomas, whereas those in which the lymphocytic elements outnumber the epithelial elements are apt to be considered as lymphoblastomas or lymphosarcomas.

CLINICAL FEATURES

Thymic tumors are slow-growing and may be present for years without producing symptoms. They do not metastasize. Their clinical course in no way resembles that of a carcinoma or lymphoblastoma. If a thymic tumor is completely removed there is no danger of recurrence. Finally, thymic tumors do not respond as well to deep roentgen therapy as do lymphoblastomas.

At the Mayo Clinic during the period 1935 through 1949 forty-five patients with tumors that were classified as thymomas based on tissue obtained by surgical operation or post-mortem examination were observed. In thirty-four, or 75.6 per cent, the patient with a thymic tumor had myasthenia gravis. The youngest patient was sixteen years of age, the oldest sixty-eight. The average age of all patients in the series was about forty-four years. There were twenty-eight females and seventeen males. Symptoms that might be ascribed to the presence of a thymic tumor were remarkably few. There was no evidence of obstruction of the trachea or bronchi, and in only three cases were there signs of superior vena caval obstruction. Pain in the chest, probably due to involvement of parietal pleura by the tumor, occurred in eight patients. Since complete surgical removal of the thymic tumor was possible in only three of eight patients who had experienced pain in the thorax, the presence of this symptom must be viewed with concern.

ROENTGENOLOGIC ASPECTS

There are no features in the roentgenologic appearance of thymic tumors to distinguish them from other tumors that can occur in the anterior mediastinum. However,



Fig 31-1. Mass in the right middle lobe of the thymus of a patient with myasthenia gravis. The tumor proved to be a thymoma. (Left) Posteroanterior view. (Right) Right lateral view.

in only two instances in the authors' experience have thymic tumors occurred elsewhere than in the anterior mediastinum. In one patient a thymic tumor was found lying posterior to the superior vena cava in the mid-mediastinum; in another the thymic tumor was found in the parenchyma of the right lung (Figure 31-1). Castleman and Norris have noted that thymomas can develop in ectopic situations and mention one case in which a thymic tumor was found on the anterior surface of the left bronchus. They express the belief that ectopic situations of thymic tissue can be readily explained embryologically. Most thymomas are located in the anterior mediastinum anterior to the arch of the aorta but they may occur at a lower level and even approach the diaphragm.

Thymic tumors are usually round or oval

and rather sharply circumscribed but may be flattened over the pericardium (Figure 31-2). Sufficient calcium to be apparent roentgenologically was present in thirteen of forty-five tumors in our series. It was usually in the periphery of the tumor but in some instances was distributed throughout the tumor. The presence of calcium in a thymoma does not mean that the tumor is completely benign. In several cases in which calcification had been noted roentgenologically, operation disclosed an inoperable invading type of tumor.

All patients known to have or suspected of having myasthenia gravis should have a very thorough roentgenologic investigation with posteroanterior and lateral roentgenograms and roentgenoscopy. Furthermore, all patients with myasthenia gravis should be



Fig 31-2. Typical roentgenographic appearance of thymoma in the lateral view. a. Right lateral view of a small, ovoid, anterior mediastinal thymoma. b. Left lateral view of a flattened, ovoid anterior superior mediastinal thymoma. c. Left lateral view of a typical thymoma in the anterior superior mediastinum.



Fig. 31-3. Roentgenographic appearance of thymoma in the posteroanterior view. *a.* Thymoma projecting into the right side of the thorax. *b.* Thymic tumor projecting into the left side of the thorax. *c.* Large thymic tumor projecting into the left side of the thorax.

examined roentgenologically at least once a year subsequent to a negative result on roentgenologic examination, because thymic tumors may develop after myasthenia gravis has been present for years (Figure 31-3).

PATHOLOGIC ASPECTS

On the basis of gross or microscopic examination, it is impossible to distinguish the thymoma removed from the patient with myasthenia gravis from the thymic tumor removed from a patient not afflicted with myasthenia gravis. Thymomas vary in size from that of a small nodule to that of a tumor filling the mediastinum and bulging into the pleural space. One of the largest removed by the authors was $10 \times 10 \times 15$ cm. and weighed 700 Gm. (Figure 31-4a).

Most are only a few centimeters in diameter (Figures 31-4b and 31-5). It is unlikely that it would be possible to recognize roentgenologically a thymic tumor less than 2 cm. in diameter.

The tumor may be solid, or partially or almost completely cystic (Figure 31-6). In three instances it was not possible to identify tumor cells in the walls of cystic thymic lesions and only the fact that the cyst was removed from the anterior superior mediastinum of a patient afflicted with myasthenia gravis justified the inclusion of these cases among the series of thymic tumors. Typically, a thymic tumor is a lobulated tumor with a thick capsule that is usually complete. However, in about one fourth of our cases the capsule was incomplete and the tumor had

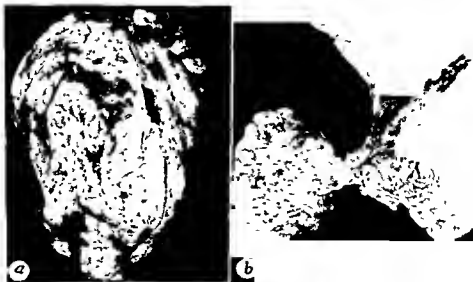


Fig. 31-4. *a.* Huge encapsulated thymic tumor weighing 700 Gm. and measuring $10 \times 10 \times 15$ cm. *b.* Thymus with a tumor of the right lower pole.



Fig 31-5 Thymus with a tumor of the left lower lobe.

invaded contiguous structures in the mediastinum. On cut surface the thymoma is grayish-pink or yellow, and fibrous trabeculae are a prominent feature. Regions of calcification may be noted in the capsule or trabeculae. The cysts may contain a thick, white, puttylike material, old blood, or serosanguineous fluid.

The behavior of thymic tumors is unusual. They tend to extend by invasion but do not metastasize by the blood or lymph streams. In ten of our forty-five cases, the tumor had invaded contiguous structures. The pleura was invaded in six cases, the pericardium in

five, the superior vena cava and innominate veins in five, and the lung in three. In two cases the tumor had spread to pleural surfaces by implantation. Histologically it has been impossible to differentiate those tumors that showed invasive tendencies from those which were well encapsulated. In eleven cases of thymic tumor in which complete necropsies were performed, there was no evidence of lymphogenous or hematogenous spread. No case was observed in which extension of a thymic tumor outside the thoracic cage had occurred.

Thymomas are slow-growing tumors. In this series of forty-five cases several instances were observed in which the tumor had been present for four to as long as ten years. One patient has been followed who has had a thymic tumor too invasive to be removed for five years and the patient was still alive at last report.

Whether thymomas are to be considered benign or malignant depends on one's definition of malignancy. Castleman and Norris consider them benign neoplasms. Certainly the dense capsule, cystic changes, calcification, and slow growth suggest that they are benign. Likewise, the microscopic picture is not that of a very malignant tumor. On the other hand, a tumor that can invade through parietal and visceral pleura directly into the lung, and through the pericardium into the



Fig 31-6 a. Almost complete cystic degeneration of a well-encapsulated thymoma. (From W. O. Seybold, J. R. McDonald, O. T. Clagett, and C. A. Good [9], courtesy of *Journal of Thoracic Surgery*. b. Partial cystic degeneration of a thymic tumor. c. Cut surface of a solid, well-encapsulated thymoma.



Fig. 31-3. Roentgenographic appearance of thymoma in the posteroanterior view. *a.* Thymoma projecting into the right side of the thorax. *b.* Thymic tumor projecting into the left side of the thorax. *c.* Large thymic tumor projecting into the left side of the thorax.

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Fig. 31-4 *a.* Huge encapsulated thymic tumor weighing 700 Gm. and measuring $10 \times 10 \times 15$ cm. *b.* Thymus with a tumor of the right lower pole.



Fig 318. Sections of thymomas stained with hematoxylin and eosin a Vessel surrounded by areolar tissue with palisaded epithelial cells ($\times 500$). b. Fibrous trabecula with the epithelial cells palisaded at right angles to the long axis of the trabecula ($\times 165$) c Typical thick fibrous capsule and cystic spaces, some of them small, some large, lined by epithelial cells ($\times 3$) (From W. D. Seybold, J. R. McDonald, O. T. Clogett, and C. A. Good [9], courtesy *Journal of Thoracic Surgery*.)

pericardial cavity and into the walls of the superior vena cava and innominate veins sufficiently to cause superior vena caval obstruction, can hardly be considered an innocent tumor.

TREATMENT

There are at present only two methods of treating thymic tumors: deep roentgen irradiation and surgical resection. In our series, roentgen therapy had been used in about one third of the cases without any appreciable effect having been produced on the size of the

an excellent exposure of all the structures in the anterior mediastinum. An additional advantage is that it does not require opening of the pleural space on either side. The split sternum heals well and leaves no weakness or deformity of the thoracic cage (Figures 31-9, 31-10, and 31-11). For large thymic tumors, for thymic tumors that present chiefly into one pleural space, and for those that lie in the region of the diaphragm, a posterolateral transpleural approach is preferable. A parasternal or transcostal approach can be used for small thymic tumors that present slightly to

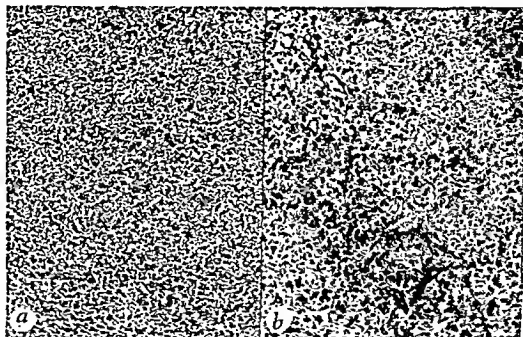


Fig 31-7. Sections of thymomas stained with hematoxylin and eosin ($\times 100$). a. The thymocyte is the dominant cell in the tumor. b. The epithelial cell is the dominant cell. (From W. D. Seybold, J. R. McDonald, O. T. Clagett, and C. A. Good [9], courtesy *Journal of Thoracic Surgery*.)

tumor. Likewise, no histologic changes in the tumors treated by the roentgen rays have been noted. It is not believed that thymic tumors are sensitive to roentgen radiation. However, it has been the practice of the authors to use intensive radiation therapy for inoperable thymomas.

The proper operative approach for removal of thymic tumors depends largely upon the size and location of the tumor as determined by roentgenologic examination. A sternum-splitting incision is preferred for small tumors that lie near the mid-line. This approach is the only one that will permit removal of the entire thymus gland, and it does provide

either side of the sternum but the exposure is not adequate in most instances and this approach has no particular advantage.

Operations for thymic tumor were carried out upon forty-one patients. In ten, or approximately one fourth of the series, the tumor could not be completely removed because of its invasion into vital structures, particularly the walls of the blood vessels in the mediastinum. Six of these patients with inoperable thymomas had myasthenia gravis, four did not. Two of the patients in this group died in the hospital. Both had myasthenia gravis; one died of complications resulting from myasthenia gravis, the other of rupture

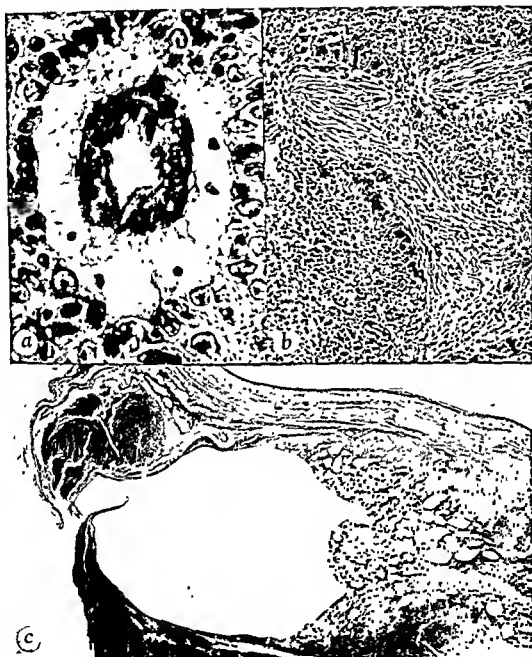


Fig. 31-8 Sections of thymomas stained with hematoxylin and eosin. *a* Vessel surrounded by areolar tissue with palisaded epithelial cells ($\times 500$). *b* Fibrous trabecula with the epithelial cells palisaded at right angles to the long axis of the trabecula ($\times 165$). *c* Typical thick fibrous capsule and cystic spaces, some of them small, some large, lined by epithelial cells ($\times 5$) (From W. D. Seybold, J. R. McDonald, O. T. Clagett, and C. A. Good [9], courtesy *Journal of Thoracic Surgery*)

of the ascending aorta, which occurred when a thymic tumor was peeled away from the wall of the aorta. In thirty-one patients, thymic tumors were completely removed. In some the entire thymus gland was removed with the tumor, in others only the thymoma itself was removed. Removal of the entire thymus gland

myasthenia gravis, the third from pulmonary complications. This last patient did not have myasthenia gravis. Five patients whose thymomas had been completely removed died from myasthenia gravis after complete recovery from the operative procedure. There have been no deaths of patients whose thymic

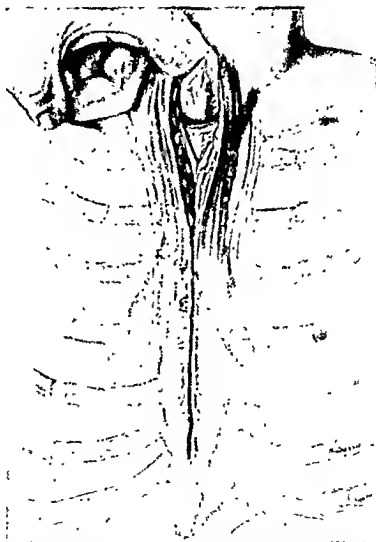


Fig. 31-9. Sternum-splitting incision. The finger is inserted behind the manubrium to push soft tissues back before inserting the bone chisel.

together with the thymic tumor seems to offer no particular advantage, so far as the patient is concerned, over removal of the tumor alone. In the group of patients whose thymomas could be removed completely, none has died because of recurrence of or distant metastasis from the tumor after dismissal from the hospital. There were three postoperative deaths among the thirty-one patients whose thymomas were removed; two died from their

tumors were completely removed and who did not have myasthenia gravis.

PREOPERATIVE AND POSTOPERATIVE MANAGEMENT OF THE MYASTHENIC PATIENT

Since thymic tumors are associated with myasthenia gravis in 75 per cent of cases, careful management of the myasthenic patient who is to undergo surgical treatment is

pertinent. Actually the major risks involved in operations for thymic tumor are incident to the presence of myasthenia gravis.

Myasthenia gravis may present an extremely varied clinical picture and course. The symptoms are those that result from a pecu-

made to improve the patient's nutritional status before operation. Usually, however, adequate doses of neostigmine will permit a patient to ingest a satisfactory diet. Occasionally it may be necessary to resort to tube feeding. Because of the difficulty in swallow-

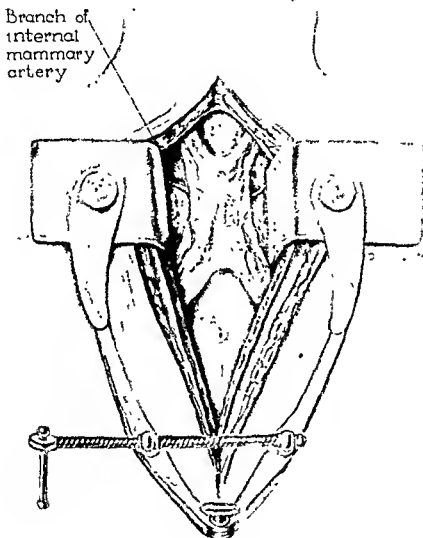


Fig. 31-9 (Contd.). Split sternum separated and anterior mediastinum containing thymus exposed (From O. T. Clagett, L. M. Eaton, and R. P. Glover [2], courtesy Surgery)

liar fatigability and weakness of voluntary muscles. Any muscle or group of muscles may be involved but the muscles concerned with eye motion, facial expression, chewing, swallowing, and talking are affected most frequently.

Because of difficulty in chewing and swallowing, many of the patients are thin, weak, and poorly nourished. Every effort should be

ing, these patients sometimes aspirate food or oral secretions into their air passages. The best protection against this is adequate neostigmine therapy. Every precaution should be taken to protect them against respiratory infection, to which they are very susceptible and which often causes severe exacerbations of myasthenia gravis. The amount of neostigmine administered to any myasthenic patient

is determined by the severity of the disease. In this regard myasthenia gravis is similar to diabetes. The myasthenic patient soon learns to judge his neostigmine requirement much as the diabetic patient learns to estimate his insulin needs. Without neostigmine to aid in controlling the severe manifestations of the disease, it would be impossible to perform

nitrous oxide, oxygen, and ether administered through an intratracheal tube. Thiopental (Pentothal) sodium is a respiratory depressant and should be avoided. Curare and any medication containing quinine are strictly prohibited. These agents cause severe exacerbations of myasthenia and are very dangerous. An intratracheal tube permits aspiration of

Inferior thyroid a

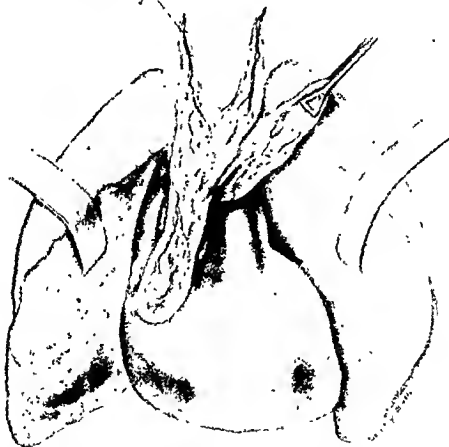


Fig. 31-10. Diagrammatic sketch showing relation of the thymus to the heart, lungs, and great vessels.

operations on most patients who have myasthenia gravis.

A period of a few days in the hospital before operation is advisable for all myasthenic patients. Heavy sedation should be avoided at all times. Just before going to the operating room the myasthenic patient should be given 1.0 to 1.5 mg. neostigmine methylsulfate, 8 mg. morphine sulfate, and 0.43 mg. atropine sulfate.

The anesthetic agent of choice for patients with myasthenia gravis is a combination of

secretions from the tracheobronchial tree during operation and prevents any difficulty that might result should the pleura be opened during operation. Neostigmine is available at all times and should be administered hypodermically if any sign of respiratory difficulty develops during operation. There is little shock or loss of blood in most operations.

The postoperative period requires strict vigilance. The margin of safety for some of these patients is not great and they may require large doses of neostigmine postopera-

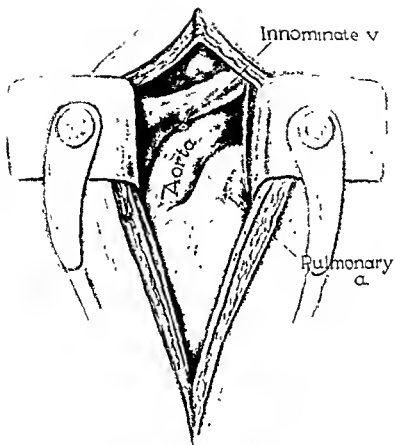


Fig 31-10 (Contd). Anatomy of the anterior mediastinum after removal of the thymus. (From O. T. Clagett, L. M. Eaton, and R. P. Glover [2], courtesy Surgery)



Fig 31-11. Closure of the split sternum with interrupted sutures in the periosteum and fascia of the sternum. (From O. T. Clagett, L. M. Eaton, and R. P. Glover [2], courtesy Surgery.)

tively. It may be necessary to administer 1.0 to 1.5 mg. of neostigmine methylsulfate every hour or two for the first twelve to eighteen hours postoperatively in some cases. Oxygen therapy may be indicated. An aspirator should be available to remove any accumulation of secretions in the nasopharynx and to prevent the aspiration of them into the tracheobronchial tree. Any evidence of anxiety, dyspnea, or respiratory embarrassment should be looked on with greatest concern since it is a sign of impending danger. A Drinker type respirator should be readily available whenever a myasthenic patient is operated on and any patient who shows evidence of exhaustion or respiratory difficulty should be placed in the respirator immediately, even though his or her general condition appears to be good. While a patient is in the respirator, it is safe

to administer larger doses of sedative agents, if necessary, than it would be wise to give to a myasthenic patient under ordinary circumstances. Equipment should be available for aspiration of the tracheobronchial tree, or for bronchoscopy if there is evidence that secretion is accumulating in the air passage that the patient is not able to raise. If patients are not able to swallow satisfactorily during the postoperative period, a tube should be inserted through the nose into the stomach for administration of adequate fluids and nourishment. In most of the authors' patients the postoperative course has not been difficult, but it is wise to be prepared for any eventuality. The course of these patients is unpredictable. Most patients are up and about within forty-eight hours and leave the hospital in ten or twelve days.

Tumors of the Heart

Ivan D. Baronofsky
and
Lawrence I. Zaraff

Until the last few years a discussion of tumors of the heart would have been considered, for the most part, academic. Now, with the rapid development of pump oxygenators and open heart surgery, a study of these growths is of vital importance. It is now feasible to diagnose, with angiocardiology, as well as remove many intracavitary tumors of the heart.

CLASSIFICATION OF TUMORS OF THE HEART

Tumors of the heart may be classified as follows:

- A. Intracavitary
 1. Polypoid
 - a. Myxoma
 - b. Organized thrombus
 - c. Fibroma
 2. Sarcoma
- B. Mural (including subendocardial and subepicardial layers)
 1. Lipoma
 2. Rhabdomyoma
 3. Angioma
 4. Sarcoma
- C. Extramural
 1. Teratoma
 2. Dermoid
- D. Pericardial
 1. Fibroma
 2. Lipoma
 3. Neurofibroma
 4. Cysts
 5. Sarcoma
 6. Carcinoma
- E. Secondary

1. Metastatic
2. Contiguous

DESCRIPTION OF COMMON TUMORS OF THE HEART

Polypoid Tumors

MYXOMA AND/OR ORGANIZED THROMBUS

The pedunculated, circumscribed, myxomatouslike masses within a cavity of the heart (Figures 32-1 and 32-2) are considered by some to be true neoplasms [48] while others do not ascribe a neoplastic nosology to them [55]. Probably both types exist.

Grossly they vary in size from that of a



Fig. 32-1. Pedunculated myxoma of the left auricle. (From R. M. Lymburner [36]. Graduate School Thesis, University of Minnesota.)



Fig 32-2. Pedunculated myxoma of the left auricle, bisected, showing hemorrhagic areas in the substance of the tumor. (From R. M. Lymburner [36], Graduate School Thesis, University of Minnesota.)

tiny 5 mm. nodule to as large as 5 cm. in diameter, are attached by a pedicle, and are intracavitary. They may be smooth and rounded, lumpy or polypoid, and villous. They are usually pale yellow, bluish-gray, or yellowish-brown, often having hemorrhagic areas on the surface, and sometimes being partly covered with fibrin. Thrombi sometimes overlie the surface of the tumor. On cut section the tumors are gelatinous and frequently hemorrhagic (Figures 32-3, 32-4, and 32-5).

They usually arise from the endocardium of the left auricle. They may either originate from a valve or block a valve by engaging in the orifice. The predilection of this tumor is for the region of the foramen ovale. Prichard [46] studied this peculiarity and found that the region contains most of the connective tissue in the heart, and might be expected to be the site of most connective tissue tumors (Table 32-1).

TABLE 32-1.—DIFFERENTIATION OF MYXOMA AND ORGANIZED THROMBUS*

<i>Myxoma</i>	<i>Organized thrombus</i>
1. Smooth surface and transparent	1. Granular surface and opaque
2. Gelatinous consistency	2. Stratification
3. Stroma uniform with vessels and cells well developed	3. External portion composed of organized tissue with abundant extravasation (Stahr)
4. Absence of hemosiderin	4. Abundant hemosiderin, presence of fibrin (DeVecchi)
5. Star cells	5. Layers of cells of inflammatory origin (Brenner)
6. Localized to both auriculoventricular valves and to the foramen ovale	6. Located anywhere within the two atria
7. Mucin	7. No mucin
8. Elastic fibers usually central (Bergstrand)	8. Elastic fibers of tumor joining with those of endocardium

* After A. Fabris [19].

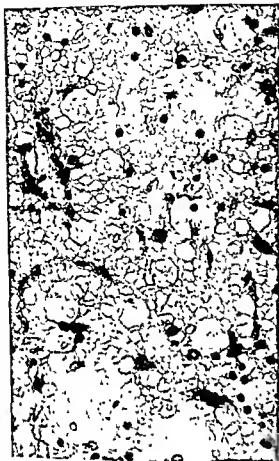


Fig 32-3. Photomicrograph of myxoma demonstrating the distribution of mucin (X 330). (From R. M. Lymburner [36], Graduate School Thesis, University of Minnesota.)

FIBROMA

In general, this tumor again is a debatable one. Many authors consider it of the same nature as a myxoma or an organized thrombus. Fibromas are usually single, pedunculated, small, and located on the valves, having arisen from their subendothelium. The tumors are common, occurring in about 20 per cent of hearts. Yater [59] states that when one considers the highly papillary structure, the smooth, shining surface, and the fact that the growth usually occurs on a normal valve, the idea of a connective tissue tumor seems logical. On the other hand, he states that if Ribbert's [48] assumption is correct (that mucoid tissue ends developmentally as connective tissue), then one may consider these growths also as myxomas. Mahaim [37] reviewed 250 cases of polyps of the atrium through 1940. The incidence between the two atria is compared in Table 32-2.

TABLE 32-2—A COMPARISON OF POLYPOID TUMORS WITHIN THE ATRIA OF THE HEART

Type	Left atrium	Right atrium	Total
Indeterminate	41	11	52
Thrombus	45	11	56
Myxoma	68	14	82
Sarcoma (primary)	10	10	20
Secondary neoplasm	12	12	24
Fibroma	8	0	8
Angioma	3	1	4
Lipoma	1	3	4
Total	188	62	250

SOURCE: I. Mahaim [37].

Sarcoma

Sarcoma of the heart is not too uncommon. Mahaim [37] records 87 collected cases from the literature to 1942. Anatomically the growth may be intracavitary, mural, pericardial, or mixed. Histologically these tumors may be spindle-celled, round-celled, giant-celled,



Fig 32-4. Photomicrograph of myxoma showing the fine fibrous connective tissue (X 165). (From R. M. Lymburner [36], Graduate School Thesis, University of Minnesota.)



Fig. 32-5. Photomicrograph of myxoma showing the presence of elastic tissue ($\times 200$) (From R. M. Lymburner [36], Graduate School Thesis, University of Minnesota)

myxomatous, mixed-celled, angiomatous, or lymphomatous. There is a curious predilection of this tumor for the atria (61 cases) and particularly for the right atrium (42 cases). It must be recalled that myxomas also prefer the atria, preferably the left. Why the malignant growths should arise from the right side and the benign from the left is impossible to answer. To suggest that oxygen tension, which is lower in the right heart blood, may have an effect on the malignant tendency is pure conjecture. In the 87 collected cases of Mahaim the apparent location of the original tumor was: right atrium, 29; left atrium, 15; right ventricle, 4; left ventricle, 3; left and right atria, 4; left and right ventricles, 3; left atrium and ventricle, 3; right atrium and ventricle, 5; both atria and both ventricles, 4; left ventricle and septum, 2; right ventricle and septum, 1; interventricular septum, 3; pulmonary artery, 8; aortic valves, 1;

entire heart, 1; myocardium (origin undetermined), 1.

Many of the sarcomas in Mahaim's collected series were polypoid in nature. Might it not be possible that these tumors are merely late stages of formerly benign growths? The common origin of malignant tumors of the intestinal tract from polyps is well documented. In fact, it might be well to apply lessons learned in the latter field to tumors of the heart, i.e., to remove polyps if possible. As absurd as this may sound at this early date, it is well to remember that we are in an era when intracardiac manipulations are rather common.

The size of sarcomas of the heart varies considerably; however, they are usually large, because they are recognized late in their clinical course. Metastases may occur to any organ of the body. The most common sites are the lungs, pericardium, mediastinal lymph



Fig. 32-6. Photomicrograph of rhabdomyoma of the heart showing the numerous large multinucleated cells ($\times 75$). (From R. M. Lymburner [36], Graduate School Thesis, University of Minnesota.)

nodes, adrenals, and kidneys. The frequent involvement of the pericardium and pleura leads to hemorrhagic effusions in the majority of cases. Many of the cases reported in the literature were explored surgically, only to find that the agent causing the effusion was an extensive sarcoma of the heart. The presence of effusion may aid in the differential diagnosis between this tumor and primary pericardiac tumors [57].

Sarcomas of the heart may occur at any age, most of them occurring between the ages of twenty and sixty years. They seem to be equally distributed between the sexes.

Lipoma

Lipoma of the heart is a rare tumor of little clinical interest. Usually lipomas are mural but they may be intracavitary. In a case reported by Brewis the tumor was attached by a pedicle on the intraventricular septum and completely obstructed the tricuspid orifice. The lipomas are usually small, but may develop to reach 4 cm. in diameter. Thorel [55] suggests their origin from clusters of fatty tissue that can be seen occasionally under the endocardium of the right ventricle, the septum, and rarely of the left ventricle. Kirch-Hertel [34] reports a case with many lipomas of the mural type associated with multiple tumors of the body. Histologically these tumors do not differ from the ordinary variety of lipomas.

Rhabdomyoma

This interesting heart neoplasm was first described by von Recklinghausen [47] in 1862 (Figure 32-6). Steinbiss [53] suggested that because of the frequent association of similar malformations in other organs, rhabdomyomas are phenomena of a general developmental disturbance due to an abnormal germ condition. According to Steinbiss, the tumor cells preserve morphologically the embryonal type but reach a high degree of tissue maturity. Bundschuh [10] believed that this tumor originates from a primitive layer common to the Purkinje fibrils and the myocardial cells before differentiation into the two muscle systems has taken place. Yater [59] has pointed out that this theory is strengthened by the fact that rhabdomyoma fibers may

show a transition into the myocardial fibers at the periphery of the tumor. The opinion has been expressed that rhabdomyomas of the heart represent a localized type of von Gierke's disease (glycogen storage disease).

There are three morphologic types of rhabdomyomas. (1) solitary, (2) multiple,

TABLE 32-3—PATHOLOGIC CONDITIONS ASSOCIATED WITH RHABDOMYOMA OF THE HEART

<i>Pathologic condition</i>	<i>Instances</i>
Tuberous sclerosis of brain	26
Kidney tumors	10
Polycystic kidneys	8
Adenoma sebaceum of skin	4
Congenital anomalies	4
Neurologic nests in brain and spinal meninges	1
Porrocephalus	1
Negative	9
No details	5
Brain not examined	2

Source: R. M. Lymburner [36], Graduate School Thesis, University of Minnesota.



Fig 32-7. Lymphangioma of the right auricle. (From R. M. Lymburner [36], Graduate School Thesis, University of Minnesota.)



Fig. 32-5. Photomicrograph of myxoma showing the presence of elastic tissue ($\times 200$). (From R. M. Lymburner [36], Graduate School Thesis, University of Minnesota.)

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Sarcomas of the heart may occur at any age, most of them occurring between the ages of twenty and sixty years. They seem to be equally distributed between the sexes.

Lipoma

Lipoma of the heart is a rare tumor of little clinical interest. Usually lipomas are mural but they may be intracavitary. In a case reported by Brewis the tumor was attached by a pedicle on the intraventricular septum and completely obstructed the tricuspid orifice. The lipomas are usually small, but may develop to reach 4 cm. in diameter. Thorel [55] suggests their origin from clusters of fatty tissue that can be seen occasionally under the endocardium of the right ventricle, the septum, and rarely of the left ventricle. Kirch-Hertel [34] reports a case with many lipomas of the mural type associated with multiple tumors of the body. Histologically these tumors do not differ from the ordinary variety of lipomas.

Rhabdomyoma

This interesting heart neoplasm was first described by von Recklinghausen [47] in 1862 (Figure 32-6). Steinbiss [53] suggested that because of the frequent association of similar malformations in other organs, rhabdomyomas are phenomena of a general developmental disturbance due to an abnormal germ condition. According to Steinbiss, the tumor cells preserve morphologically the embryonal type but reach a high degree of tissue maturity. Bundschuh [10] believed that this tumor originates from a primitive layer common to the Purkinje fibrils and the myocardial cells before differentiation into the two muscle systems has taken place. Yater [59] has pointed out that this theory is strengthened by the fact that rhabdomyoma fibers may

show a transition into the myocardial fibers at the periphery of the tumor. The opinion has been expressed that rhabdomyomas of the heart represent a localized type of von Gierke's disease (glycogen storage disease).

There are three morphologic types of rhabdomyomas. (1) solitary, (2) multiple,

TABLE 32-3—PATHOLOGIC CONDITIONS ASSOCIATED WITH RHABDOMYOMA OF THE HEART

<i>Pathologic condition</i>	<i>Instances</i>
Tuberous sclerosis of brain	26
Kidney tumors	10
Polycystic kidneys	8
Adenoma sebaceum of skin	4
Congenital anomalies	4
Neurologic nests in brain and spinal meninges	1
Porencephalus	1
Negative	9
No details	5
Brain not examined	2

SOURCE: R. M. Lymburner [36], Graduate School Thesis, University of Minnesota.



Fig. 32-7. Lymphangioma of the right auricle. (From R. M. Lymburner [36], Graduate School Thesis, University of Minnesota.)

TABLE 32-4.—DISTRIBUTION OF RHABDOMYOMA IN THE HEART: 47 CASES

<i>Lt. aur.</i>	<i>Lt. vent.</i>	<i>Rt. aur.</i>	<i>Rt. vent.</i>	<i>Intervent. septum</i>	<i>Intra-auric. septum</i>	<i>Mult. sites</i>	<i>Site not stated</i>
1	27	4	19	9	1	12	0

Source. R. M. Lymburner [36], Graduate School Thesis, University of Minnesota

and (3) diffuse. The solitary nodule is usually located at the apex of the heart and is unassociated with other developmental abnormalities. The multiple nodules are usually mural and may or may not project into the cavities of the heart or the pericardial sac. They are often associated with other developmental conditions (Table 32-3).

The tumor seems to be equally distributed between the sexes and the predominant age incidence in post-mortem series is the first decade of life. The distribution of the rhabdomyoma in the heart in Lymburner's [36] collected series of cases is shown in Table 32-4.

Angioma

True angiomas of the heart are rare. Penneman [43] described a hemangioendothelioma on the anterior wall of the left auricle, about the size of a chestnut, cystlike in character, and projecting into the cavity of the auricle. Grant and Camp [24] described an arterial angioma located in the membranous portion of the interventricular septum. This tumor had malignant tendencies, as it destroyed the common trunk of the bundle of His-Tawara, provoking a complete atrioventricular block.

Lymphangiomas of the heart (Figures 32-



Fig. 32-8. Photomicrograph of lymphangioma through the pedicle. The connective tissue of the tumor is continuous with that of the surface of the auricle ($\times 73$). (From R. M. Lymburner [36], Graduate School Thesis, University of Minnesota)

7 and 32-8) have been reported by Uehlinger [56] and by Lymburner [36]. In the latter's case the heart tumor, interestingly enough, was associated with a lymphangioma of the neck. The heart lesion was probably formed from the lymphatic channels of the auricular surface of the heart.

Nicod [40] in 1945 described an angio-reticuloma of the heart situated near the foramen ovale. The peculiarity of this tumor is its close resemblance to the "hemangioblastoma" as described by Cushing and Bailey [15] in the central nervous system. Roussy and Oberling [49] realized this close resemblance and suggested the name "angio-reticuloma" in order to suggest its dual origin (1) from the blood vessel itself, and (2) from the penvascular reticular tissue.

Armstrong and Mönekeberg [1], Perry and Rogers [44], Lloyd [35], and Mahaim [37] have described tumors of the node of Tawara, which appear as a lymphangioendothelioma-like type. Mahaim suggested that these tumors are of embryonic character and are essentially due to malformation occurring during the twisting of the heart in its early embryonic development to become a four-chambered organ from a single tubular one. He prefers the name "coelothelioma of Tawara." Of importance is the fact that the tumors are secretory in character and may, therefore, cause disturbances of the conduction system if they become large enough or cause inflammatory changes.

Varices, varicose veins, blood nodes, and blood cysts have been described; they are entirely benign and cause no symptoms.

Primary Pericardiac Tumors

Primary tumors of the pericardium are rarer than tumors of the heart proper. They may be composed of any element that constitutes the pericardium proper. Thus, fibromas, lipomas, neurofibromas (phrenic nerve), cysts (pleuropericardial), sarcomas, and even carcinomas have been described.

Of particular academic interest are the reported carcinomas. They contain a connective tissue framework with many blood vessels interspersed. They are indeed very similar to the tumors of other serous-lined cavities and the meninges. Mahaim suggests the term

"coelothelioma malin" and offers the following embryologic deviation:

Somatic mesoderm

1. Myoepithelium (voluntary muscle)
2. Somatic mesenchyme (bone, cartilage, and connective tissues)

Visceral mesoderm

1. Visceral mesenchyme (vessels and supportive muscles)
2. Coelomic epithelium (serous coverings, meninges, and epithelial portions of the genitourinary tract)



Fig. 32-9. Roentgenogram of calcified cyst removed by Dr. C. Beck. The wall of the cyst shows deposition of calcium and some reduction in size. (From C. Beck [3], courtesy *Annals of Surgery*)

Primary dermoid and teratomatous tumors situated within or attached to the pericardium are of rare occurrence [27]. Joel [31] reported a teratoma attached to the root of the pulmonary artery. Mouat [38] reported a dermoid that apparently arose from the pericardium and produced caval obstructive symptoms. Grimm [25] as well as Jellen and Fiseher [30] have also reported these cases. It would appear that in most of the patients the relationship between parietal pericardium and the wall of the cyst was not clear. Beck [3] reported the removal of a primary teratoma of the heart that appeared to have become an indistinguishable part of the pericardium—the first instance of the successful removal of such a primary tumor (Figures 32-9, 32-10, 32-11, and 32-12). In 1957, Daggs, Peirce, and Rawson [16] reported the successful removal of an intrapericardial teratoma in one stage. The



Fig. 32-10. Appearance one year after operation (same patient as Figure 32-9). The cardiac silhouette is normal. (From C. Beck [3], courtesy *Annals of Surgery*.)

tumor was also correctly diagnosed preoperatively by angiocardiology.

In 1930, Keller and Callender reported the successful removal of a neurofibroma that was attached to the pericardium by a broad base along the course of the phrenic nerve. Hochberg and Robinson [28] in 1950 reported the



Fig. 32-11. Artist's interpretation of relationship between teratoma, right ventricle, right auricle, aorta, and vena cava. (From C. Beck [3], courtesy *Annals of Surgery*.)

successful removal of a cavernous hemangioma of the pericardium.

Metastatic Tumors of the Heart and Pericardium

Tumors metastatic to the heart and pericardium occur about twenty to forty times more frequently than primary growths [46]. Secondary tumors of the pericardium occur more frequently than secondary tumors of the heart.

The neoplasms in the heart and pericardium are similar to those found in other organs,



Fig. 32-12. Photograph of a teratoma removed from within the pericardium. (From C. Beck [3], courtesy *Annals of Surgery*.)

i.e., small, whitish, firm nodules diffusely or discretely scattered throughout the myocardium. Sarcomatous metastasis to the myocardium may be of a diffuse nature with complete replacement of the muscle. Metastases sometimes grow sufficiently large to encroach on the chambers. The valves are occasionally involved. It would be easy to explain carcinomatous involvement of the valve as one might explain bacterial endocarditis, i.e., by contaminated blood constantly passing over the region; yet, in many instances, histologic sections of the valve show only a few cancer cells, if any at all. Eger [18] reviewed 12,705 autopsies, in which he found 446 instances of valvular lesions, of which 169 were of the verrucous type. There

Tumors of the Heart

was no cancerous involvement of the valves, although 45 of the 169 patients had an associated cancer. The pericardium may be involved by infiltration, with thickening, often in such cases there is a fibrinous exudate in the two layers and a hemorrhagic or non-hemorrhagic effusion. In rare cases the superficial lymph vessels of the heart and pericardium are involved in a carcinomatous lymphangitis and stand out as whitish threads.

A predilection for right-sided involvement of the heart by metastases has been suggested. Yater [59] offered an explanation for this finding based on a blood-vascular basis, i.e., most of the venous drainage to the heart eventually drains into the right side. Embolic tumor cells may thus have more opportunity to lodge on the right than the left.

Not the least important of secondary tumors of the heart are those that extend onto the heart or pericardium by contiguity. Thus, tumors of the bronchi, lungs, esophagus, thyroid, thymus, and any other mediastinal structure may directly invade the heart and its coverings. From a surgical standpoint this type of tumor has been removed frequently. Mahaim calls attention to a peculiar bradycardia (passive nodal rhythm), which is obtained in those cases of esophageal tumor. This, he explains, is due to the involvement of the Keith-Flack node by the esophageal tumor.

Another peculiar secondary tumor is the neoplastic thrombus. This tumor usually originates at a distance from the heart and grows into the afferent venous return (caval system) and then actually extends into the heart. Thus, Judd and Scholl [32] have reported a renal tumor that extended into the inferior vena cava and continued to grow up and into the right auricle. These tumors will, naturally, present in the right side of the heart. However, cases have been reported of secondary tumors lodging in the lung and then growing into the pulmonary veins and then into the left auricle.

INCIDENCE OF CARDIAC TUMORS

Primary Tumors

Primary cardiac tumors are rare. Lymburner [36] states that in the course of 8,550

consecutive autopsies at the Mayo Clinic, four primary tumors of the heart were encountered, none of which was malignant. Strauss and Merliss [54] estimate the incidence of primary cardiac tumors to be 0.0017 per cent of autopsied cases. Whorton [57] has recorded three instances of primary cardiac tumors in a series of 20,337 autopsies. Of 329 cases of collected primary tumors that Mahaim recorded from the literature, 87 were malignant (Table 32-6).

Secondary Tumors

Scott and Garvin [51] found 101 cases of secondary cardiac tumors in 1,082 autopsies. Burke's [11] series of 327 cases yielded fourteen instances. Willis [58] records twenty instances in 323 autopsies. Pollia and Gogol [45] noted 29 secondary cardiac tumors in 1,450 autopsies. Lymburner noted 52 cases in 8,550 autopsies. Prichard [46] recorded cardiac metastases 326 times in 8,414 autopsies. The totaled incidence is about 2.3 per cent. Forty-four per cent of patients dying of malignant melanoma have metastases in the heart (Paek [42]). Recent studies, pointed out by Hurst [29] in 1955, indicate that of 1,264 patients dying of cancer, cardiac spread was found in 20 per cent. The most common origins of metastases were the breast and lung; these organs produced cardiac metastases in one of three cases. In the series reported by Bisei, Wroblewski, and LaDue [7] from Memorial Hospital (New York), 44 per cent of patients dying of leukemia and 24 per cent of those with lymphoma had involvement of the heart.

SIGNS AND SYMPTOMS OF CARDIAC TUMORS

General Symptoms

Yater has classified the symptomatology of cardiac tumors as follows:

A. Clinical types not suggestive of heart tumor

1. Absence of symptoms referable to the heart
2. Symptoms of cardiac embarrassment terminally
3. Symptoms of congestive heart failure
4. Sudden death

TABLE 32-5.—RELATIVE NUMBER OF CASES OF METASTATIC TUMORS OF THE HEART,
WITH DISTRIBUTION ACCORDING TO PRIMARY SITE
(Total Cases 4,375—Total Cardiac Metastases 146)

Carcinoma		Sarcoma	
Breast	23	Lymphatic system	18
Lung	16	Bone	2
Stomach	9	Penis, stomach, kidney, peripheral nerve, spleen, undetermined (1 each)	6
Cervix uteri	7	Total	26
Kidney	7		
Tongue	6	Melanoma (cancerous)	
Rectum	4	Skin	12
Penis	3	Eye	4
Esophagus	3	Vulva	1
Ovary	3	Anus	1
Testis, bladder, mouth (2 each)	6	Total	18
Vagina, liver (hepatoma, cholangiocar- cinoma), prostate, thymus, lip, antrum, brachial cleft, pharynx, uterus, thy- roid, sigmoid, scrotum, pancreas (1 each)	14		
Total	101		

SOURCE R. W. Frichard [46], courtesy A. M. A. Archives of Pathology.

5. Symptoms suggestive of subacute bac-
terial endocarditis
- B. Clinical types suggestive of heart tumor
 1. Heart block
 2. Symptoms referable to location of the
tumor other than heart block
 3. Symptoms of cardiac dysfunction de-
veloping without apparent cause in a
patient with known malignant tumor
 4. Accumulation of hemorrhagic fluid,
pericardial and pleural
 - 5 Suggestive roentgen observations

Mahaim recorded thirty instances through 1945 in which the correct diagnosis of heart or pericardial tumor was made. With angio-
cardiography, the diagnosis will be made more
often. The clinical manifestations that do
occur are encountered with other mediastinal
tumors that may obstruct the inflow to the
heart with distention of the neck veins, edema,
of the face, upper trunk, and upper extremi-
ties, and the development of collateral circula-
tion. Instances of inferior caval obstruction
have been noted.

Specific Tumor Symptoms

LEFT AURICULAR POLYPS AND THROMBI

According to Mahaim [37], left auricular
polyps and thrombi are suggested by the fol-

lowing signs and symptoms: (1) intermittence
and the paradoxical variations of signs of re-
gurgitation owing to movement of tumor in
and out of the mitral orifice; (2) paradoxical
variations of signs of stenosis according to
position of the patient; (3) variations in the
murmur of mitral regurgitation; (4) syncope
due to intermittent occlusion of the mitral or-
fice with resultant reflex tachycardia; (5)
failure of cardiac drugs to improve the symp-
tomatology; (6) concomitant psychic disorders
due to intermittent cerebral anemia; (7)
embolic symptoms—when an embolus has
been removed and been histologically diag-
nosed as of myxomatous appearance, it is
pathognomonic.

Mahaim has classified left auricular polyps
into three types, depending on the signs: Type
I, which gives signs of pure mitral stenosis;
Type II, in which signs of regurgitation are
also present; Type III, in which the polyp is
also associated with an organic mitral lesion.

SARCOMA

Since the symptomatology of cardiac sar-
coma is dominated by its localization in the
right auricle, the following signs and symp-
toms are suggestive: (1) superior vena caval
obstructive signs; (2) inferior vena caval ob-
structive signs; (3) absence of bronchial
and pulmonary signs; (4) pericardial effusion

Tumors of the Heart

with hemopericardium and cells present in the pericardial fluid; (5) cardiac arrhythmias; (6) embolic phenomena with biopsy of the emboli.

CONTIGUOUS TUMORS

Contiguous tumors are suggested by: (1) the demonstrated presence of mediastinal tumor; (2) the sudden appearance of cardiac arrhythmias; (3) diagnostic pericardiocentesis demonstrating hemopericardium.

DIAGNOSIS OF CARDIAC AND PERICARDIAC TUMORS

In general, it is difficult to diagnose cardiac tumors and pericardiac tumors. Some aids to

SURGICAL RATIONALE AND TREATMENT

Surgical Rationale

TUMORS OF THE HEART

Since the development of open heart surgery with pump-oxygenators (Figure 32-13), and hypothermia, the surgical removal of tumors of the heart has become possible. The first successful removal of an intra-atrial myxoma was performed by Crafoord on July 16, 1954, with extracorporeal circulation. Since then, Bahnson [2], Gerbode [21], and Hanlon [26] have successfully removed myxomas with the aid of pump-oxygenators.

TABLE 32-6.—MAHAJIM'S TABLE OF PRIMARY CARDIAC TUMORS STUDIED BY HIM AND COLLECTED FROM THE LITERATURE

	<i>Polypoid tumors</i>	<i>Nonpolypoid tumors</i>	<i>Total</i>
Cardiac			
Myxomas	82	23	105
Fibromas	8	29	37
Lipomas	4	10	14
Angiomas (and lymphangiomas)	4	9	13
Rhabdomyomas		60	60
Coelotheliomas		5	5
Miscellaneous (benign)		8	8
Sarcomas	21	66	87
Total	119	210	329
Pericardiac			
Fibromas	7		7
Lipomas	3		3
Angiomas	10		10
Miscellaneous (cysts)	19		19
Coelotheliomas	24		24
Sarcomas	20		20
Indeterminate (malignant)	1		1
Total	84		84

Source: I Mahajim [37].

the diagnosis have been suggested. Thus, pneumopericardium, angiocardiology with outline of the heart and large vessels, pericardiocentesis, and electrokymography all may be of definite value. Any method should be invoked that will aid in the establishment of the diagnosis, and with the recent advent of cardiac catheterization, it may be possible to localize more accurately neoplasms of the heart.

Bigelow [6], Scannell [50], and Chin [13] have removed similar tumors under hypothermia.

Mahajim, in his exhaustive review, studied 413 cases of primary cardiac and pericardiac tumors (Table 32-6). Of the primary tumors of the heart, 119 were polypoid; of these, twenty-one were sarcomas, which for the moment we will consider inoperable, leaving a remaining ninety-eight. In addition to those presented, he was able to find fifty-six that

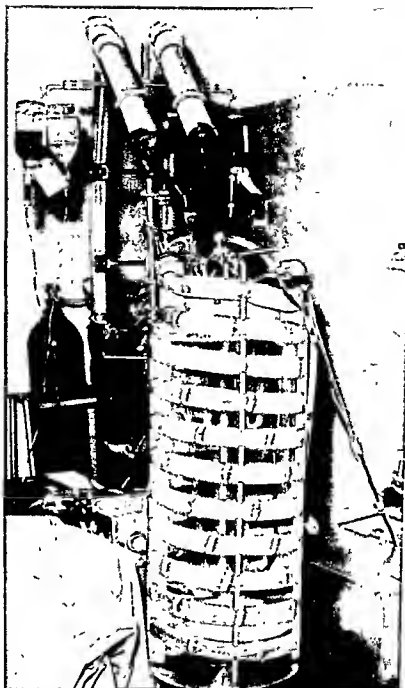


Fig. 32-13. Photograph of a pump-oxygenator (DeWall) that may be used for the removal of tumors of the heart

he did not record because of their indeterminate nature and fifty-two that consisted of pure clot-ball thrombi, giving a total of two hundred six polypoid and pseudopolypoid lesions. All were either cavity-obliterating or near cavity-obliterating. They are certainly within the realm of surgical attack by the technic which will be described. Polypoid tumors of the heart should no longer be

considered as medical curiosities and objects of pathologic arguments, but as surgical entities, just as are polypoid lesions of the colon.

Consideration must also be given to certain other primary tumors of the heart. Thus, if one were to localize a sarcoma of the heart that was polypoid in nature and causing cavitory obstructive symptoms, there is no reason to believe that removal of such a

tumor might not be possible and perhaps life-saving. With modern surgical advances there is no reason to believe that a nonpolypoid tumor of the ventricle itself might not be resected with a portion of the ventricle. Experimentally, Gordon Murray has resected portions of dogs' hearts that have been infarcted by previously placed ligatures.

Tumors located in the myocardium have already been resected by Beck [3] and by Hochberg [28]. Certainly, if a patient presents symptoms due to an intrapericardial tumor that seems to be well localized, every effort should be made to remove it. Even if these tumors may prove to be unresectable, it may be entirely possible to provide for a new shunt around it, such as Gerbode has done by anastomosing the superior vena cava to the right auricular appendage.

TUMORS OF THE PERICARDIUM

Pericardiac tumors have been resected. The entire pericardium has been removed on numerous occasions, both experimentally and in human beings. Pericardial decortication, as performed for chronic constrictive pericarditis, is a successful operation. The pericardium is now being removed as a further step in the management of pulmonary cancer [41].

TUMORS SECONDARY TO NEOPLASMS OF CONTIGUOUS ORGANS

Mention should be made of secondary tumors of the heart, particularly tumors of thoracic organs contiguous with the heart. Carcinoma of the lung occasionally will invade or extend onto the heart or pericardium. Portions of the heart, such as the pericardium and the auricles, have been resected if they have been involved and the pulmonary cancer has been resectable.

OPERATION FOR BIOPSY PURPOSES

Another reason for operation in tumors of the heart or pericardium is for biopsy purposes. In the event that a tumor may not be resectable, a portion of it may be obtained and studied. When the pathologic diagnosis has been obtained, it may prove to be a radio-sensitive tumor; therefore, adequate radiation therapy may be instituted.

Surgical Procedures

APPLICATION OF HYPOTHERMIA AND PUMP-OXYGENATORS

The removal of tumors of the heart has been greatly facilitated by the successful application of hypothermia and pump-oxygenators to heart surgery. It is now generally agreed that these tumors should be removed under direct vision with the aid of the above-mentioned technics.

The rapidly changing aspects of open heart surgery, especially those concerned with technic, physiology, and preoperative and postoperative care, make it unwise at this time to prescribe a concise method. Suffice it to say that if surgery for these lesions is contemplated in the present or future, a practiced team of people must be set up. This team must practice as a unit in the experimental laboratory until it functions as a unit. The type of pump-oxygenator, if this is preferred to hypothermia, is arbitrary. There are a great number now available. Each type must be thoroughly tested (Figure 32-13).

A TRIOCAVAL ANASTOMOSIS FOR LESION-PRODUCING OBSTRUCTION OF SUPERIOR VENA CAVA (GERBODE)

The superior vena cava is approached with the patient in a left lateral decubitus position. The cava is mobilized by incising the pleura along its margins, permitting the separation of the tissues from its posterior wall. The pericardium ascends for several centimeters on the lower end of the superior vena cava. Its sac is incised over the lower end of the cava, allowing the upward reflection of pericardium to be cleared from the vein by sharp dissection. This incision, when carried downward, exposes the right auricle. A few cubic centimeters of 1 per cent procaine hydrochloride is applied to the surface of the auricle. The superior vena cava above the tumor is then clamped with vascular clamps (Pott's ductus clamps). Another clamp is placed about 2 to 3 cm. above this clamp and the cava transected between these two clamps. The distal stump is then oversewn with continuous arterial silk. The auricular appendage is picked up with toothed forceps, a rubber-covered clamp is applied across its base, and

a small piece of the tip of the auricular appendage is excised with scissors. The end of the superior vena cava is then anastomosed to the opening in the auricle, using a continuous everting silk suture. A few interrupted

RESECTION OF THORACIC TUMORS THAT HAVE BECOME CONTIGUOUS WITH THE HEART

In the removal of tumors of the thoracic organs it is sometimes necessary to resect

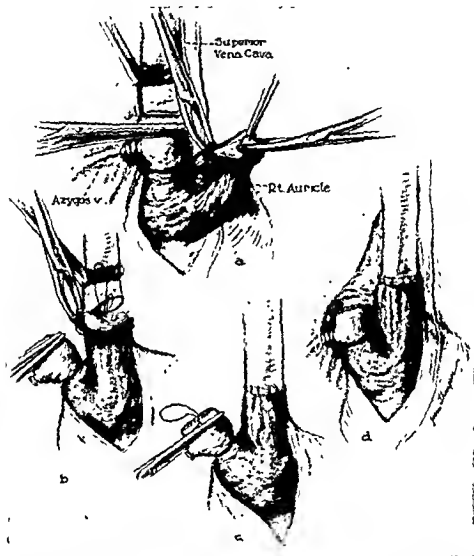


Fig. 32-14. Technique of anastomosing the superior vena cava to the right auricle (Gerbode). *a* The superior vena cava has been transected above the level of the azygos vein, the right auricular appendage is grasped with a rubber-covered clamp while the tip is excised, thus creating a lumen into the atrium. *b* A continuous everting suture of arterial silk is used. A broad cuff is everted so that none of the cut edge of the auricular muscle remains in the lumen. *c* The anterior row is reinforced with a few interrupted sutures. The stump of the superior vena cava is closed with a double row of arterial silk. *d* The completed anastomosis (From F. Gerbode, J. Yee, and F. F. Rundle [22], courtesy Surgery)

sutures are added to the anterior row. The clamps are then removed. The pericardium is approximated over the anastomosis with several interrupted sutures (Figure 32-14).

portions of the heart and pericardium. Thus, in pulmonary cancer, in order completely to remove the tumor, it at times becomes necessary to remove a portion of the atrium. It

would be impossible to designate a single method of approaching this heterodox type of surgery, except to state that adequate vascular instruments should be present and the fundamentals of vascular suturing be known. Many clinics are now reporting such removals as a routine procedure [41] in the attempt to cure cancer of the lung and other intrathoracic cancers.

EMBOLECTOMY

This procedure will not be described here. We mention it only to say that some tumors of the heart will throw off emboli. These may lodge in portions of the peripheral arterial system and endanger life or limb. In spite of the prognosis because of the primary tumor, every effort should be made to remove the offending embolus.

Tumors of the Chest Wall

R. Arnold Griswold
and
James C. Drye

The chest wall should be considered an organ of the respiratory system. Its functions are to furnish an adequate respiratory exchange and to protect the underlying viscera. To perform these functions it must be able to make its contained volume alternately smaller and larger, it must not leak, and it must be of adequate thickness and rigidity. These vital functions must be preserved.

The blood supply of the chest wall is, fortunately, segmental, with profuse collateral channels, and rarely imposes restrictions on excision. The lymphatic supply has not been worked out in detail. However, most of the primary chest wall tumors are sarcomas and do not often spread by way of the local lymphatics, and when they do spread in this manner, there are usually distant metastases. In the occasional case in which resection of the chest wall is done for carcinoma, the paravertebral and retrosternal lymph nodes should be removed.

Benign tumors usually can be simply shelled out or locally excised, leaving a small defect. However, if the benign tumor is large and requires disruption of the chest wall, the problem of maintenance of the function exists.

In this chapter we will deal with those tumors of the chest wall which, because of their size or their malignancy, require excision of the wall to such an extent that special techniques are needed to restore the basic functions.

The published statistics on the incidence of chest wall tumors are inaccurate. There have been more than five hundred primary chest wall tumors reported and apparently a

little over half of these have been malignant.

Theoretically, tumors may arise from any of the tissues that make up the chest wall. In the collected reviews of Sommer and Major [29] and of Dörner and Marcy [7] and in the large personal series of Blades and Paul [3] there are almost 25 different types of tumors reported in about 160 cases. Chondrosarcomas are the most common malignant tumors. Fibrosarcomas, malignant neurilemmomas, and Ewing's tumor occur less frequently. There are other rare malignant tumors. Among the benign tumors, chondromas, osteomas, neurilemmomas, and lipomas occur most often.

DIAGNOSIS OF TUMORS OF THE CHEST WALL

The two most common and reliable symptoms of chest wall tumors are pain and a lump in the chest wall. Of the two, pain is the more reliable and constant, as the growth may protrude but little and pain may develop before a mass is recognizable either clinically or, more rarely, by x-ray. The pain is usually dull and boring and not affected by respiration early in the disease. Later it may become pleuritic when the tumor involves the pleura. Severe pain occurs more often in malignant tumors. However, pain is not a reliable criterion to differentiate between benignity and malignancy.

The lump may be present for years and never change size, or it may be present for many years and suddenly start to grow, or it may grow rapidly throughout its course.

Proper x-rays are by far the most helpful

of all diagnostic procedures in chest wall tumors. As a rule, the ordinary AP, PA, and lateral projections are all that is necessary. In special instances tangential, stereoscopic, and sectional x-rays may be required.

At times pneumothorax and/or pneumoperitoneum may be very helpful. They may demonstrate whether the tumor has invaded the diaphragm, the lung, or the abdominal viscera.

In many cases a general bone survey will be helpful in demonstrating the multiple bone lesions of polyostotic fibrous dysplasia, multiple myeloma, metastatic cancer, and the lesions of hyperparathyroidism.

Biopsy by the aspiration method is preferred by us. There have been no well-authenticated cases of dissemination of the tumor by aspiration biopsy except in cases of malignant melanoma. An excisional biopsy or even an incisional biopsy should be done before radical surgery is justified. In either case, the wound should be tightly closed to prevent contamination of the subsequent operative field with malignant cells. If the pathologist can give an accurate diagnosis from a frozen section of the biopsy, the decision as to the proper procedure can be made at that time. If he feels that permanent sections are necessary, one should wait for the more accurate diagnosis. In most institutions permanent section can be finished in twenty-four to forty-eight hours; this short wait will not influence the prognosis.

PRIMARY CHEST WALL TUMORS

Sarcomas

Sarcomas are the most common neoplasms arising in the chest wall. Chondrosarcoma, osteogenic sarcoma, fibrosarcoma, and Ewing's sarcoma are encountered most frequently.

From published reports it is impossible to get an accurate cure rate because of the almost complete lack of follow-up of more than a year. Many are simply reported as having survived operation. In the combined reports of all sarcomas subjected to operation to 1948, there were only four of 103 patients known to have survived five years free of cancer. Blades and Paul [3] in 1950

reported two cures in twenty patients. The more recent results are probably better. These tumors are rare and it takes a long time to collect a series that is large enough to be statistically significant and has gone for five years or more.

Osteogenic sarcoma, fibrosarcoma, and Ewing's sarcoma, when arising in the chest wall, behave much as they do elsewhere.

TREATMENT

The treatment, except for Ewing's sarcoma, is wide excision. This excision in all cases should include the entire thickness of the chest wall, including the pleura. Any involved rib should be removed from the vertebral articulation to its sternal attachment. When arising in the sternum, the entire segment in which the tumor originates or which it invades should be excised.

When possible, adherent structures should be resected in whole or in part. Adherence to a lobe of the lung demands lobectomy if cure is to be expected. Likewise, adherence to the diaphragm calls for adequate resection of that part of the diaphragm. When the sarcoma is adherent to such structures as the aorta, extensive adherence to the spine, or other nonresectable structures, the case is incurable.

Ewing's Sarcoma

Ewing's sarcoma may occur in the bones of the chest wall. These tumors behave here much as they do elsewhere, with the additional findings of dyspnea, pleurisy, and pleural effusion as the cancer progresses. They occur invariably before the age of thirty years. (See Vol. VIII for a general discussion of Ewing's sarcoma.)

TREATMENT

There is no close agreement as to the method of treatment. Blades believes that operation is of no value and that irradiation alone should be used. He advises that in suspected but unproved cases surgical biopsy be obtained. While rapidly prepared histologic sections may be difficult to classify as to the exact nature of the malignant cells, Ewing's sarcoma and the lymphomas can be identified. If such tumors are found, the operation is

terminated and roentgen therapy instituted. Kinsella [19] advises a combination of operative removal and postoperative irradiation.

In the series of eighteen cases reported by Sommer and Major [29], fourteen patients were reported dead; ten of the fourteen died thirteen months or less after treatment; four died three, two, three, and six years, respectively, after treatment. Of the four patients not known to be dead, one was living with sarcoma six months after treatment, and one was living and well two months after treatment; follow-up data were not given on two patients.

On studying the above case reports, there is no significant difference seen in the length of survival following different methods of treatment.

Cartilaginous Tumors

The cartilaginous tumors—chondrosarcoma, myxosarcoma, osteochondroma, and chondroma—arise most often from the costal cartilages. About one fifth of them arise from the sternum and a few from the articular cartilages of the vertebra. (See Vol. VIII for a discussion of cartilaginous tumors.)

TREATMENT

In reviewing the reported cases of alleged benign chondroma, we are greatly impressed by three facts. First, the vast majority of these cases have been followed for one year or less. Second, in those patients who have been followed for five years or more, recurrence and final change into chondrosarcoma have been almost the rule. Third, a large number of patients had very limited resections. In a report by O'Neal and Ackerman [24], only fifteen of ninety-six patients with cartilaginous tumors were known to be alive and free of recurrence for more than two years. What is even more striking is that of these fifteen two-year cures, seven were from the group of fifty-eight patients with chondrosarcoma and only eight were from the group of forty-one who were thought to have benign tumors. In view of these findings we believe that all chondromas arising in the chest wall should be clinically regarded as malignant and that complete and wide excision should be done at the time of the first surgical attack.

Cartilaginous tumors may often appear

very benign histologically, much more benign than the enchondromas arising in the small bones of the hands and feet (Geschickter [9]). Although it is well known that simple local excision with curettage will cure a number of the latter tumors, similar limited attacks will be met with recurrence in chondromas of the chest wall. This is merely another instance in which clinical experience does not agree with the histologic structure.

We believe that cartilaginous tumors require wide excision of all layers of the chest wall, including the pleura. If the tumor arises in the ribs, long segments should be excised. Upshaw, McDonald, and Ghormley [35] showed that infiltration may extend out from the gross limits of the tumor as far as three inches in the marrow cavity. If the tumor arises in the sternum, the entire segment involved should be removed completely.

Tumors of Nerve Trunk Origin Arising in the Chest Wall

These tumors are fairly common. In Blades's series [3], after exclusion of lipomas they accounted for 45 per cent of the benign tumors. They occur most often in the paravertebral gutter and have long been classed with posterior mediastinal tumors. However, they occur occasionally further out along the nerve trunks.

Most are neurilemmomas, either diffuse or encapsulated [33]. The diffuse type may occur as an isolated growth but is found often as a manifestation of von Recklinghausen's disease. The encapsulated type is usually a solitary encapsulated tumor attached to a nerve. It is not usually associated with von Recklinghausen's disease but about 18 per cent [32] do occur in frank or suspected cases of this disease. Either may recur locally or undergo malignant change but this is much more common in the diffuse type, in which the incidence of malignant change is about 13 per cent [10].

Surgical biopsy is usually impractical in those tumors lying deep in the paravertebral gutter and aspiration biopsy may be misleading.

TREATMENT

Proper treatment is wide and complete excision.

When these tumors occur in the chest wall as a part of von Recklinghausen's disease, they should be removed only if the tumor shows rapid growth, which is presumptive evidence of malignant change, or if the tumor is causing local symptoms and can be removed as a palliative measure.

Myeloma of Bone

Multiple myeloma runs its normal course within a few months to an average of two years after diagnosis. Solitary myelomas are unpredictable in their behavior. Christopher and Miller [6] collected twenty-two well-authenticated cases followed for more than three years, and fifteen followed from one to three years, which remained localized for the total time of observation. One case in each group occurred in a rib.

TREATMENT

Radical surgical removal is not indicated in either type. It is useless in multiple myeloma and unnecessary in the solitary type. The latter can be surgically treated by simple local excision or curettage. This has provided known survivals ranging between nine and sixteen years [6]. Radiation therapy also gives excellent results.

Giant-Cell Tumors of the Chest Wall

Giant-cell tumors rarely involve the bones of the chest wall. There were ten cases reported from 1914 to 1950 (Buckles and Lawless [4]), with no recurrence reported in any of these ten patients. Six of the ten were living after eleven years; two more were living at five months and twenty-two months, respectively. One patient sustained an operative death, and one died of a proved bronchogenic carcinoma at 2.5 years. Six of the ten were treated by excision alone, two by biopsy and irradiation, and two by excision and irradiation. One, who died in the immediate post-operative period, was considered to have a malignant giant-cell tumor. Samson and Haight [27] advised irradiation in proved cases. Buckles advises early surgical excision.

Vascular Tumors of the Chest Wall

Superficial benign hemangiomas are not considered here (see Vol. IX).

Hemangiomas arising in the deep tissues of

the chest wall are rare. They have been reported in the ribs and in the subcutaneous tissue. When arising in the ribs, they have produced pain, local mass, and rib destruction (Kinsella [19]). They may simulate osteolytic sarcoma. Although there may be lesions in other bones, they are really benign. The treatment is resection of the involved rib in its entirety.

The hemangiomas arising in the soft tissues are usually benign but may be of the malignant variety, i.e., hemangioendothelioma. Blades and Paul [3] reported one case in which the patient died of generalized metastases after resection. When lying deep to the skin, the characteristic color and compressibility may not be observed. They may produce only a soft bulky mass and be mistaken for lipoma. They should be widely excised. If there is any suggestion of malignancy, the excision should include all layers of the chest wall.

Lipoma

Small, superficial lipomas present no problem. Large lipomas, even if they are apparently superficial, should be treated with respect. Appropriate x-ray studies with pneumothorax may be necessary to rule out a large intrathoracic component of the tumor.

SECONDARY TUMORS OF THE CHEST WALL

Metastatic Neoplasms

Tumors metastatic to the chest wall are common. They most frequently arise from neoplasms primary in the breast, prostate, cervix, kidney, and thyroid. Frequently there is widespread metastatic involvement that makes such patients not amenable to surgery. At times, however, a tumor in the chest wall is the only metastasis that can be found. It may arise from a primary neoplasm that has been or can be locally controlled. The primary tumor may be obvious, or it may be occult and suspected only after histologic study of the metastasis. In the latter case, the metastasis is at first frequently mistaken for a primary tumor.

Many of these occult primary tumors occur in the kidney or the thyroid gland and produce osteolytic metastases that may pulsate

[2, 3, 17]. The pulsation has been so marked in some cases as to simulate an aneurysm [17]. Griswold [12], in 1947, resected a pulsating tumor of the sternum. The pyelograms were negative. The clinical diagnosis was hemangioma. Histologic studies showed the tumor to be a renal-cell carcinoma. The patient died in the early postoperative period and the primary cancer was found in the kidney at autopsy.

TREATMENT

The value of resecting an apparently solitary metastasis is highly debatable. Although the salvage rate is low, there have been a few apparent cures [29]. If the risk and morbidity are not excessive, radical resection may be worthwhile. Under such conditions, little can be lost.

Locally Recurrent Breast Carcinoma

After radical mastectomy, carcinoma of the breast recurs in the operative field in 5 to 10 per cent of the patients in whom the cancer was thought to be localized to the breast, and in 20 to 40 per cent of the patients with axillary metastases [37]. This means that there is an enormous number of women who have cancer of the chest wall.

What percentage have local recurrence without metastases is not known. It must be very low. White [38], in his experience at Roosevelt Hospital in New York City, had seen only one case up to 1951. Radical operation for locally recurrent breast cancer goes back to the time of Schede in 1885, but there has been little said of the results obtained other than that the patient did or did not survive operation.

TREATMENT

Radical resection for locally recurrent breast carcinoma has been revived by Maier [22] and by Pickrell, Kelley, and Marzoni [26]. Maier's paper is limited to a statement of the problems of reconstruction of the chest wall under such conditions and the solution of these problems. No final results are given. Pickrell and his associates also present successful methods of dealing with these defects. They reported three cases of recurrent cancer of the breast treated by radical excision of the

chest wall. Two of these were reported only to the time of discharge from the hospital; one was free of recurrence at twenty months. Long-term results of other workers are not reported. The worth of radical resection of the chest wall for recurrent breast cancer is yet to be determined. It is yet to be demonstrated that the cure rate is of such order as to make the procedure worthwhile.

We are of the opinion that extensive local recurrence should be treated by irradiation when possible. Small, superficial tumors should be locally excised if only a few are present. We would reserve the extensive block dissection for extensive recurrence that cannot be treated by x-rays.

REPAIR OF CHEST WALL DEFECTS

The repair of surgically made chest wall defects must re-establish the functional integrity of the chest wall. There must be a solid, airtight closure. Enough rigidity must be attained so that there is little or no paradoxical respiration.

Sternal Defects

As pointed out by Bisgard and Swenson [2], major breaks in the anterior segment of the wall that result from resection of the sternum are much more significant than lateral chest wall defects because both sides of the chest are weakened. Further, unless good rigidity is obtained the heart may be directly compressed, but, probably more important, the venous cardiac return may be reduced owing to the rise of pressure in the mediastinum.

In the repair of sternal defects, the extent of the defect, the age of the patient, and the character of the bony structure of the ribs determine what type of repair should be done.

Resection of the manubrium or small portions of the sternum do not significantly impair the function of the chest wall. Kinsella resected the manubrium, a small part of the gladiolus, the medial one third of the clavicles, and the cartilages of the second and third ribs in a sixty-year-old man. He simply closed this defect with skin over the defect, with excellent results. There was little loss of stability and the patient did well.

Defects that do not completely disrupt the rigidity of the chest wall may be adequately

Tumors of the Chest Wall

closed by mobilizing the pectoral muscles and suturing them together over the defect in the mid-line. This type of repair is of value when a fairly good portion of the body of the sternum is removed, leaving the manubrium and xiphoid and most of the costal attachments. Heuer [17] reported a successful case treated in this manner, removing the lower two thirds of the body of the sternum. He stated that there was little loss of stability in his patient

gladiolus, the rigidity must be restored. This can be done by using a tantalum plate as a temporary prosthesis until sufficient fibrosis occurs to support the chest wall, or the rigidity can be attained by the use of bone grafts.

In younger individuals who have fair-sized ribs and whose ribs are of good consistency, bone grafts are preferable. As reported by Bisgard and Swenson, a section of a convenient rib is removed, this should be about one inch

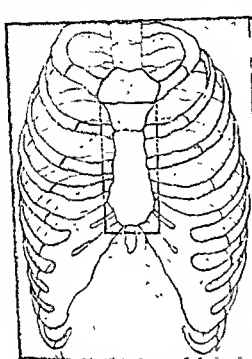


Fig 33-1. A diagrammatic illustration of the operation used to bridge the precordial defect remaining after resection of the sternum, showing the device for marissing and anchoring the grafted ribs and the manner in which these struts re-establish bony continuity to the thoracic cage (From J. D. Bisgard and S. A. Swenson, Jr. [2], courtesy *Archives of Surgery*.)

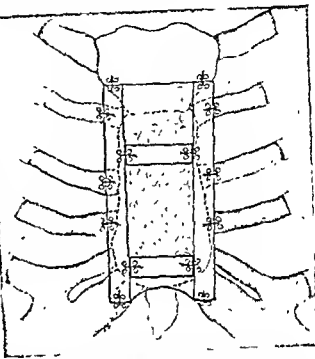


Fig 33-2. Drawing of reconstruction of the sternum by tibial bone graft and bone chips (From T. J. Kinsella, S. M. White, and R. W. Koucky [20], courtesy *Journal of Thoracic Surgery*.)

In the type of defects described above, special methods are unnecessary and little would be gained from their use.

In such limited defects, bone-grafting procedures, as advocated by Bisgard and Swenson and others and described later, are not applicable or necessary in older patients. They are indicated in younger individuals in whom better protection, rigidity, and cosmetic effects are desired. These younger people are more subject to trauma and their life expectancy is much longer.

When rigidity of the chest wall is completely disrupted by excision of the entire

longer than the defect. This is split lengthwise and peg ends are fashioned. The rib ends bordering the defect are sprung further apart and the split rib ends driven into their stumps. Further security is furnished by lashing the joint with sutures (Figure 33-1). Soft-tissue cover can be obtained by simply closing the skin. If further rigidity is desired, the pectoral muscles can be mobilized and sutured in the mid-line over the defect (Heuer).

Bone grafts from the tibia or fibula can be used in a like manner or after the manner of Kinsella [20] (Figure 33-2).

In elderly patients with small ribs and senile

osteomalacia, these bone-graft methods do not work well. The ribs are usually too small and fragile to hold the grafts. Rigidity in these patients may be achieved by the use of a tantalum plate.

It is to be emphasized that this is a temporary prosthesis. It is impossible to anchor the tantalum plate so as to prevent all movement in the tissue. Collections of serosanguinous fluid occur invariably and usually drain spontaneously through the skin incision. However, it can be left for sufficient time, i.e., about four weeks, for enough fibrosis to occur

brim, rib stumps, and xiphoid. The plate is mortised into these grooves under tension. Tantalum wire is passed through holes in the plate and around the rib stumps for added strength. The plate is covered only by subcutaneous tissue and skin.

Repair of Costal Wall Defects

Many successful methods have been devised for closure of defects of the costal portion of the chest wall. All must give sufficient rigidity to prevent paradoxical respiration and furnish an airtight closure. Consideration must be

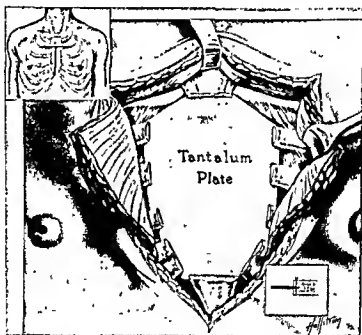


Fig. 33-3. Tantalum plate in place. The top inset shows the incision. The bottom inset shows the details of the mortising of the plate into the ribs.

to provide adequate rigidity in these elderly people. All the covering necessary is skin and subcutaneous tissue. To bring the pectoral muscles over the plate is possible, but it adds magnitude to an already extensive operation in an elderly patient.

Griswold [12] has used this temporary prosthesis with good results following the resection of the entire gladiolus and the third to the seventh costal cartilages inclusive (Figure 33-3). The plate should be at least 0.02 inches in thickness to keep it from buckling. It should be about 0.5 cm. larger than the defect. Grooves are cut in the bony portions of the edges of the defect, that is, the manu-

further given to the amount of stability and protection needed by the individual patient. A young laborer requires more stability and protection than an elderly sedentary worker. More extreme procedures are justified in the former, while in the latter the more extensive surgery is not necessary and the increased risk is not justified.

The choice of method further depends on such factors as the size and location of the defect and the condition of the soft tissue. The anterior portion of the chest is thinner, there is less muscle mass present, and it moves more than does the posterior portion. In general, it requires more stuffing than does the pos-

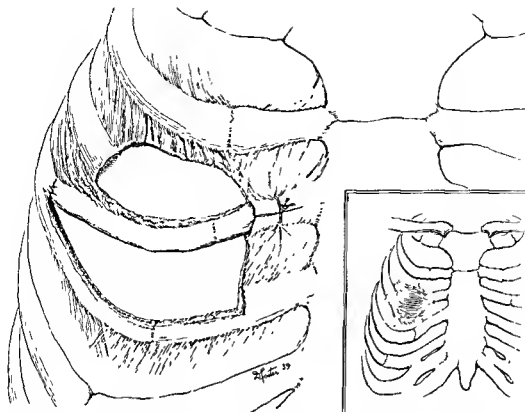


Fig 33-4. Diagrammatic representation of tumor and of method of repair of chest wall defect (From R. M. Jones [18], courtesy *Journal of Thoracic Surgery*)

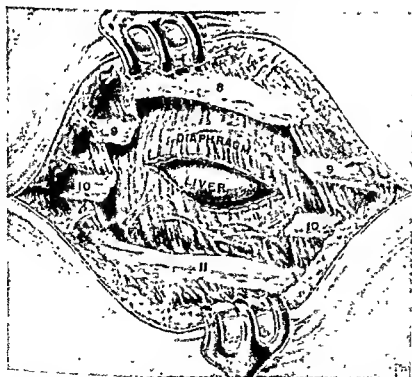


Fig 33-5 Drawing illustrating the findings at operation. Note liver present through incision in diaphragm in mid portion of defect and absence of segments of ribs nine and ten (Same case as Figures 33-6 through 33-9.) (From E. Maurer and B. Blades [23], courtesy *Journal of Thoracic Surgery*)

osteomalacia, these bone-graft methods do not work well. The ribs are usually too small and fragile to hold the grafts. Rigidity in these patients may be achieved by the use of a tantalum plate.

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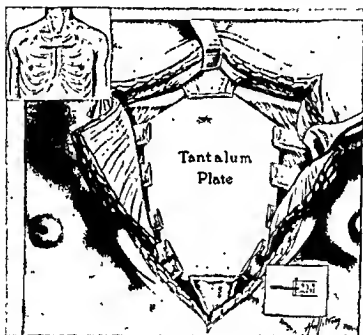


Fig 33-3 Tantalum plate in place. The top inset shows the incision. The bottom inset shows the details of the mortising of the plate into the ribs.

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The choice of method further depends on such factors as the size and location of the defect and the condition of the soft tissue. The anterior portion of the chest is thinner, there is less muscle mass present, and it moves more than does the posterior portion. In general, it requires more stiffening than does the pos-

resected rib as described by Janes [18] (Figure 33-4). Maurer and Blades [23] describe two methods in which moderately large defects can be closed using local tissue. In the first, which is more applicable to smaller defects, the intercostal bundles are simply mobilized, the periosteum is split along the rib border furthest from the defect, and the flaps are turned toward each other over the defect. The intercostal muscle bundles are sutured together and then the layer of periosteal flaps is sutured over this. In their second method, which is applicable to somewhat larger defects, the

wall defects can be closed by tissue locally present. The methods described above are well suited to all but the largest defects. They give enough rigidity to prevent paradoxical respiration and they give good stability and excellent protection that is needed in vigorous men particularly laborers.

However, in women and elderly or sedentary workers simpler methods will give enough rigidity to prevent significant paradoxical respiration and give a good airtight closure, even in large defects; for example, removal of one entire rib and generous portions

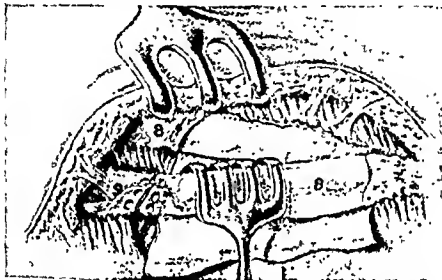


Fig 33-8 Illustrating method used to pull the eighth rib into position over the defect and to fix it in place with No. 1 chromic catgut sutures placed through small drill holes in corresponding positions at the end of the displaced eighth rib and the posterior stump of the ninth rib. (From E. Maurer and B. Blades [23], courtesy *Journal of Thoracic Surgery*.)

periosteum of the ribs adjacent to the defect above and below is cut along the rib borders furthest from the defect and the periosteum elevated. These periosteal flaps are turned toward the defect. The ribs are then cut at an angle in such a manner that the upper rib may be swung down and attached to the stump of the nearest rib of the defect. It is held in place by wire sutures that are put through drill holes in the ribs. The lower rib is treated in a similar manner. The periosteal flaps that were previously formed are then sutured together (Figures 33-5 through 33-9). Both types of these deep repairs are then simply covered with flaps of mobilized subcutaneous tissue and skin.

As stated by Maurer and Blades, most chest

of two to four other ribs along with their periosteum and the underlying pleura. In such patients a layer of fascia lata covered with mobilized flaps of skin and subcutaneous tissue is adequate.

We recently resected the entire eighth rib and the posterior five inches of the sixth, seventh, and ninth ribs en bloc along with the lower lobe of the left lung (Figure 33-10). The part of the defect resulting solely from resection of the eighth rib was easily closed when mobilizing the intercostal bundles (Figure 33-11). The remainder of the defect, where the sixth, seventh, eighth, and ninth ribs were resected, was closed by fascia lata sutured around the edges of the defect with fine interrupted silk, as suggested by Watson

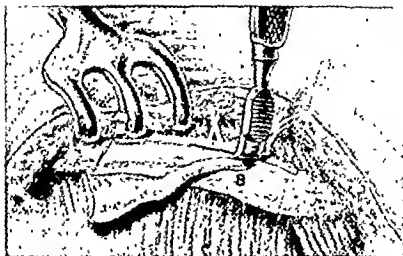


Fig 33-6. Illustrating method used in preparing a periosteal flap from the eighth rib. (From E. Maurer and B. Blades [23], courtesy *Journal of Thoracic Surgery*.)

terior portion of the chest.

Defects resulting from resection of small benign tumors present no problem. Unless the ribs are involved, simple closure of the soft tissue is all that is necessary. If short segments of one or two ribs are removed, with or without the pleura, mobilization of flaps of

skin and subcutaneous tissue may afford enough stability.

If the patient is young and vigorous or if the defect is somewhat larger, rigidity can be obtained by splitting an adjacent rib and bringing one end of the split fragment across the defect and attaching to the stump of the

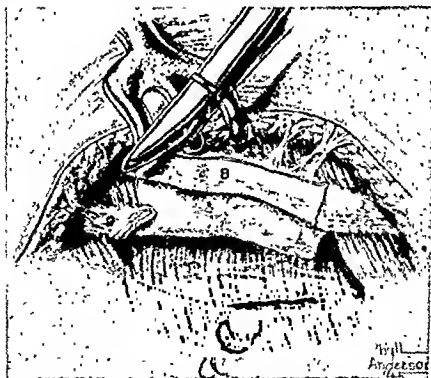


Fig 33-7. Illustrating method of cutting ribs tangentially to insure "locking." Note periosteal flap developed from the eighth rib. Incision in the diaphragm was closed with interrupted silk sutures. (From E. Maurer and B. Blades [23], courtesy *Journal of Thoracic Surgery*.)

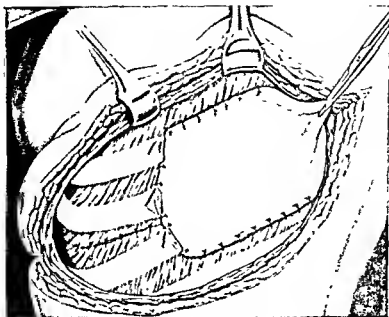


Fig 33-11 Closure of the anterior part of the defect by mobilization of the intercostal bundles. The fascia lata graft is being sutured to the edges of the larger portion of the defect

and James [37]. Flaps of skin and subcutaneous tissue were mobilized above and below. As they were brought over the defect, the fascia lata was quilted to the inner surface with fine interrupted sutures (Figure 33-12). The flaps were brought together with a deep layer of fine interrupted silk and a layer of skin flaps. The patient ran a smooth operative

course and has since had no difficulty attributable to the repair.

Large anterior chest wall defects can be similarly treated. As advocated by Campbell [5], for additional support the latissimus dorsi muscle can be swung on its attachment to the humerus, which is also, for surgical purposes, its vascular pedicle composed of the thoraco-

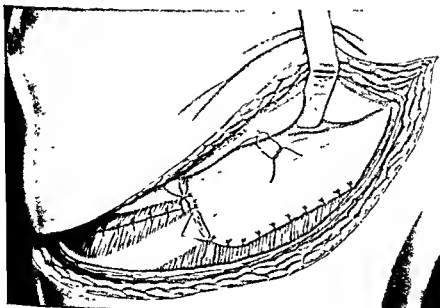


Fig. 33-12. The flap of skin and subcutaneous tissue is being brought over the fascia lata graft. The subcutaneous tissue is being quilted to the fascia lata to assure good apposition.

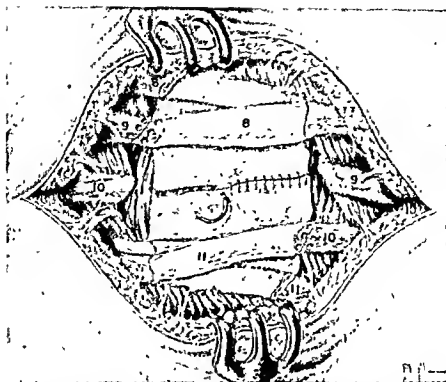


Fig 33-9. Showing the completed operation. The eighth and eleventh ribs have been cleaned of periosteum and pulled into position over the defect. Note method of immobilizing the displaced ribs accomplished by cutting through the ribs tangentially and fixing them to the rib stumps of the ninth and tenth ribs with No. 1 chromic catgut sutures placed through drill holes. The periosteal flaps were approximated under tension over the central portion of the defect. (From E. Maurer and B. Blaker [23], courtesy *Journal of Thoracic Surgery*)

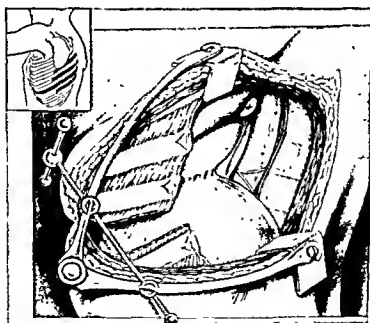


Fig 33-10. Defect present after resection of entire eighth rib and long segments of sixth, seventh, and ninth ribs and the lower lobe of the left lung. The inset shows the extent of resection. (Same case as Figures 33-11 and 33-12.)

Tumors of the Esophagus

dorsal artery and vein. This pedicle of latissimus dorsi will reach any place in the hemithorax. This procedure is usually not applicable in cases of resection for locally recurrent breast carcinoma, because this pedicle blood supply of the latissimus muscle is usually compromised by the previous radical mastectomy operation.

Moderately large defects of the anterior chest wall resulting from resections for locally recurring breast cancer require rather extensive repair. The closure of such defects is complicated by the damage to the local tissue frequently present from previous irradiation and by the absence of the pectoral muscles. The damaged tissue must be removed to get good healing. If the pleura is included in the

resection, as it usually should be, fascia lata can be sutured around the edges of the defect. This can be covered by swinging over a flap formed from the other breast, which may be brought over from a superior or inferior pedicle (Pickrell, Kelley, and Marzoni [26]). As the breast flap is brought over, the fascia lata should be quilted to the deep surface of the flap with interrupted fine sutures to assure approximation of the two layers, as the fascia lata receives its nourishment from the flaps. It may be necessary to use split-thickness skin graft to cover the region bared by the breast flaps. (For a discussion of the closure of chest wall defects following extended radical resections of the breast and chest wall, see Chap. 4.)

Treatment of Benign Tumors of the Esophagus

Stuart W. Harrington

The occurrence of benign tumors of the esophagus has been known since a very early period, as pedunculated polyps were recognized because of the periodic appearance of the tumor or its extrusion into the mouth of the patient. Their treatment is probably the earliest of recorded surgical procedures for esophageal tumors.

A great variety of benign tumors may originate in the esophagus. Among them are: adenoma, aberrant thyroid, cyst, fibroma, hemangioma, leiomyoma, mucocele, myoma, myxofibroma, lipoma, neurofibroma, papilloma, and polyp. Most authors state that polyps are the most common type of benign tumor of the esophagus; however, our experience reveals that leiomyoma is the most common benign tumor of this location.

Sussius (Susio) is credited by Minski [11] with one of the earliest necropsy descriptions (1559) of an esophageal polyp. It had extended from the middle part of the esophagus to the cardia of the stomach, causing obstruction and death. Minski also credited to Dallas and Monroe one of the earliest attempts at surgical removal, which was carried out by them in 1763 on a sixty-four-year-old patient who, on vomiting, forced multiple pedunculated tumors into the mouth, causing severe laryngeal obstruction. A preliminary tracheotomy was performed and a portion of the pedunculated tumors was ligated with a snare. Residual tumor was permitted to drop back into the esophagus. The patient was temporarily relieved but died two years later from starvation, the result of esophageal obstruction from continued growth of the remaining tumors.

PATHOLOGY OF BENIGN ESOPHAGEAL TUMORS

Benign tumors of the esophagus are of two general groups: the mucosal and the extramucosal or intramural tumors. They may arise at any point in the esophagus and may be single or multiple (Figures 34-1 and 34-2).

The mucosal tumors are of two types: lipofibromas, which usually have a single pedicle, and fibromyxomas, which often have multiple pedicles. The mucosal tumors are generally sessile and frequently become pedunculated, owing to their position and the peristaltic action of the esophagus, which tends to mold and elongate the tumor. Thus, a tumor originating in the upper end of the esophagus may extend down to the cardia or even through it and into the stomach (Figures 34-3 and 34-4). The dependent portion of the tumor is usually rounded and tapers toward the base, but it may assume various shapes and may be bifid or lobulated.

The extramucosal or intramural tumors arise from the muscle of the wall of the esophagus. Tumors arising from the outer coats of the esophagus tend to escape the peristaltic pull and seldom become pedunculated.

A benign tumor of the esophagus is usually covered with normal-appearing mucosa, although regions of ulceration may develop as a result of pressure or trauma (Figures 34-5 and 34-6). They are usually of multicentric origin. Multiple leiomyomas involving a considerable part of the wall of the esophagus or leiomyomatosis involving the entire circumference of the esophageal wall may be noted. Occasionally there is a single circumscribed

Treatment of Benign Tumors of the Esophagus

Stuart W. Harrington

The occurrence of benign tumors of the esophagus has been known since a very early period, as pedunculated polyps were recognized because of the periodic appearance of the tumor or its extrusion into the mouth of the patient. Their treatment is probably the earliest of recorded surgical procedures for esophageal tumors.

A great variety of benign tumors may originate in the esophagus. Among them are: adenoma, aberrant thyroid, cyst, fibroma, hemangioma, leiomyoma, mucocoele, myoma, myxofibroma, lipoma, neurofibroma, papilloma, and polyp. Most authors state that polyps are the most common type of benign tumor of the esophagus; however, our experience reveals that leiomyoma is the most common benign tumor of this location.

Sussius (Susio) is credited by Minski [11] with one of the earliest necropsy descriptions (1559) of an esophageal polyp. It had extended from the middle part of the esophagus to the cardia of the stomach, causing obstruction and death. Minski also credited to Dallas and Monroe one of the earliest attempts at surgical removal, which was carried out by them in 1763 on a sixty-four-year-old patient who, on vomiting, forced multiple pedunculated tumors into the mouth, causing severe laryngeal obstruction. A preliminary tracheotomy was performed and a portion of the pedunculated tumors was ligated with a snare. Residual tumor was permitted to drop back into the esophagus. The patient was temporarily relieved but died two years later from starvation, the result of esophageal obstruction from continued growth of the remaining tumors.

PATHOLOGY OF BENIGN ESOPHAGEAL TUMORS

Benign tumors of the esophagus are of two general groups: the mucosal and the extramucosal or intramural tumors. They may arise at any point in the esophagus and may be single or multiple (Figures 34-1 and 34-2).

The mucosal tumors are of two types: lipofibromas, which usually have a single pedicle, and fibromyxomas, which often have multiple pedicles. The mucosal tumors are generally sessile and frequently become pedunculated, owing to their position and the peristaltic action of the esophagus, which tends to mold and elongate the tumor. Thus, a tumor originating in the upper end of the esophagus may extend down to the cardia or even through it and into the stomach (Figures 34-3 and 34-4). The dependent portion of the tumor is usually rounded and tapers toward the base, but it may assume various shapes and may be bifid or lobulated.

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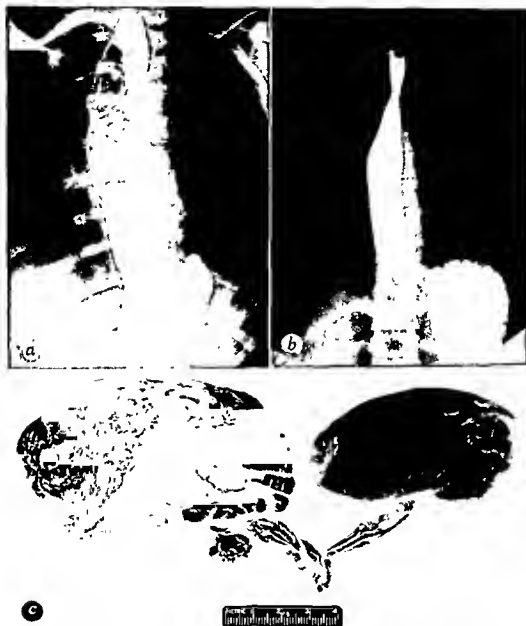


Fig 34-1. Multiple pedunculated myxofibromas in the upper half of the esophagus, for which left cervical esophagotomy was performed. *a*, On admission. The dilatation of the esophagus was originally thought to be due to cardiospasm. *b*, One month after left cervical esophagotomy. The findings with reference to the esophagus were negative and there were no symptoms. *c*, Surgical specimen. Pedunculated myxofibromas arising from the esophageal introitus (Figures 34-1a and c from S. W. Harrington and H. J. Moersch [7], courtesy *Journal of Thoracic Surgery*)

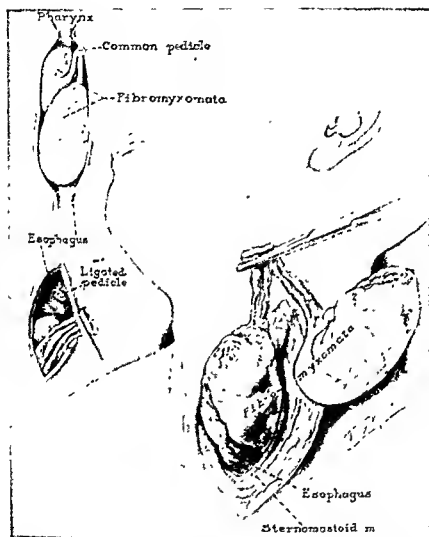


Fig. 34-2. Left cervical esophagotomy for removal of two pedunculated tumors (myxofibromas) originating from a single pedicle at the esophageal introitus

tumor. When the tumors are benign, they usually do not involve the mucous membrane, but they may undergo malignant change and invade the mucosa, causing ulceration and hemorrhage (Figures 34-7 and 34-8)

SYMPTOMS OF BENIGN ESOPHAGEAL TUMORS

The subjective symptoms and clinical manifestations are often meager, a fact that often

able. Regurgitation may take place at times and varies with the degree of esophageal obstruction. Loss of weight may occur and usually corresponds to the degree of dysphagia. Less frequently, the patient may pass blood by stool or emesis. If the tumor is large, and especially if it is of the intramural, extramucosal type, there may be a sense of substernal discomfort associated with cough and expectoration. Tumors arising in the lower



Fig. 34-3. Large, pedunculated lipoma originating from the upper part of the esophagus, for which right trans-thoracic esophagotomy was performed, with complete removal of the tumor. a. On admission. There is marked dilatation and displacement of the esophagus into the right thoracic cavity. The cordia is normal. b. Two months after right trans-thoracic esophagotomy and removal of the tumor. The esophagus is reduced in size but is still moderately dilated.

delays clinical recognition. The tumors are usually slow-growing and they may attain considerable size without giving rise to subjective symptoms. This is particularly true of the intramural tumors, which rarely produce obstruction of the esophagus unless they attain great size.

Dysphagia is the most frequent symptom. Its onset may be sudden and severe, or insidious; it is often intermittent. The size that a benign tumor of the esophagus may attain without interfering with deglutition is remark-

able. Regurgitation may give rise to a sense of epigastric discomfort.

DIAGNOSTIC METHODS FOR ESOPHAGEAL TUMORS

The diagnosis of benign tumors of the esophagus can be made with ease when the patient presents a history of regurgitation of a fleshy tumorous mass into the mouth. Roentgenologic examination of the esophagus is of great value in establishing a correct diagnosis and in differentiating a benign tumor of

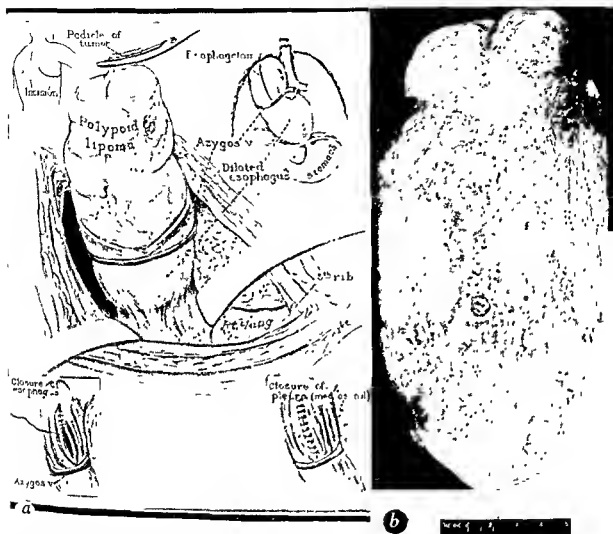


Fig 34.4 Same case as Figure 34.3. a. At operation, Transthoracic esophagotomy was performed for complete removal of the pedunculated polypoid lipoma, which was attached at the introitus of the esophagus. The upper left inset shows the posterolateral incision. The upper right inset shows marked displacement and dilatation of the esophagus and the site of the incision of the esophagus above the azygos vein. The lower left inset illustrates closure of the esophagus by the use of a continuous inverting suture of silk. The lower right inset demonstrates the completion of the closure of the esophagus and overlying mediastinal pleura with interrupted silk sutures. b. Surgical specimen. Large polypoid lipoma covered with normal esophageal mucosa that is ulcerated in places. (From S. W. Horrington and H. J. Moersch [7], courtesy *Journal of Thoracic Surgery*)



Fig. 34-5 Multicentric leiomyoma involving two thirds of the circumference of the lower 5 inches of the esophagus, treated by means of right transpleural esophagotomy, with complete removal of the tumor, including part of the mucous membrane, and reconstruction of the wall of the esophagus. a. Thorax on admission. There is a rounded mass at the cardiophrenic angle posterior to the heart shadow, considered to represent diaphragmatic hernia, mediastinal cyst, or leiomyoma. There were no subjective symptoms. b. Esophagus on admission. The tumor attached to and distorting the lower part of the esophagus on the right is probably a leiomyoma. There is a small esophageal hiatal hernia. c. Six weeks after right transpleural esophagotomy, with complete removal of the leiomyoma. There is a slight defect at the site of excision of the tumor, also, there is a small esophageal hiatal hernia which was present before operation.



Fig. 34-6. Same case as Figure 34-5. Surgical specimen. Multicentric leiomyoma measuring $10 \times 7.5 \times 5.5$ cm. and involving two thirds of the circumference of the lower 5 inches of the esophagus.

the esophagus from an extraesophageal tumor pressing upon the esophagus. However, a definite diagnosis cannot always be established by roentgenologic examination alone. This applies

even to tumors that are extremely large and that may fill the esophagus entirely.

Esophagoscopy examination is of utmost importance. The site of origin of the pedunculated tumors usually can be determined definitely. However, difficulty is encountered especially in the esophagoscopy differentiation between intramural, extramucosal tumors and extraesophageal tumors pressing upon the esophagus and deforming it.

SURGICAL TREATMENT OF BENIGN ESOPHAGEAL TUMORS

The only effective treatment for benign tumors of the esophagus is complete surgical removal. Although these tumors seldom undergo malignant change, they may do so—a fact that emphasizes the necessity for early and prompt treatment.

The earliest operations on the esophagus were of the simplest type, such as esophagotomy for the removal of foreign bodies. The earliest recorded operation of this type was



Fig. 347 Diffuse leiomyosarcoma involving the lower third of the esophagus, treated by means of left transpleural and transdiaphragmatic resection of the lower half of the esophagus and the cardiac end of the stomach, with esophagogastric anastomosis. *a* On admission. A tumor of the lower third of the esophagus extends to the cardia, displacing the esophagus to the left and causing partial obstruction (From S. W. Harrington [6], courtesy Archives of Surgery) *b* Five years after left transpleural and transdiaphragmatic resection of the lower half of the esophagus and the cardiac end of the stomach, with esophagogastric anastomosis. The esophagogastric anastomosis was patent and there were no symptoms.



Fig. 348. Same case as Figure 347. *a*. Surgical specimen. Diffuse leiomyosarcoma. *b*. Photomicrograph of leiomyosarcoma, Grade IV. (From S. W. Harrington [6], courtesy Archives of Surgery.)



Fig 34-9. Single intramural leiomyoma in the mid-third of the esophagus treated by means of left transpleural esophagotomy, with complete extramucosal removal of the leiomyoma, and reconstruction of the wall of the esophagus. *a* On admission. A filling defect is present in the right wall of the mid-esophagus, considered to represent a leiomyoma. The esophageal lesion was found during routine roentgenologic examination of the esophagus at the time roentgenograms of the stomach were being made because of suspected peptic ulcer. Roentgenograms of the stomach did not disclose any abnormality. *b*, Photograph taken at the operating table showing esophagotomy and complete extramucosal removal of a single leiomyoma in the mid third of the esophagus, measuring $7 \times 3 \times 3$ cm, and weighing 60 Gm. *c* On dismissal, three weeks after esophagotomy for the removal of a single leiomyoma and reconstruction of the wall of the esophagus. The esophagus appears normal.

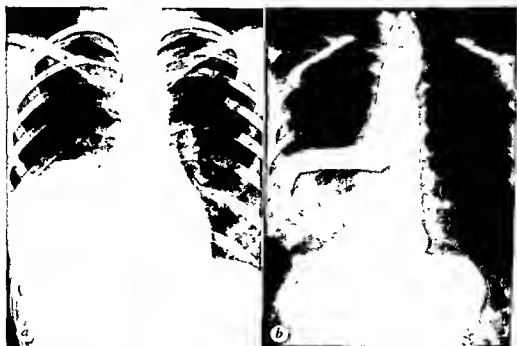


Fig 34-10. Diffuse leiomyoma of the lower third of the esophagus and the cardiac fourth of the stomach treated by means of right transpleural and transdiaphragmatic resection of the lower half of the esophagus and cardiac third of the stomach, with esophagogastric anastomosis. *a*, Tumor in the lower and mid right portions of the thoracic cavity extending to the diaphragm. *b*, Marked displacement of the lower half of the esophagus into the right thoracic cavity and questionable esophageal hiatal hernia. (*b* from S. W. Harrington [6], courtesy *Archives of Surgery*)

that of Goursauld in 1738. Because of post-operative infection, these early operations were rarely successful. No important progress was made in this field of surgery until the development of methods of preventing collapse of the lung during operation and pneumothorax after operation.

also be necessary if the pedicle of the tumor is situated low in the esophagus. (See Chaps. 35 and 36 for the details of surgical approach.)

The type of indicated operative procedure for intramural tumors cannot be definitely determined by the clinical examinations because

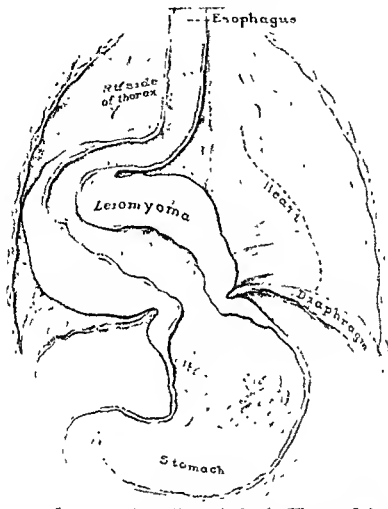


Fig. 34-11. Same case as Figure 34-10. At operation, showing position of the diffuse leiomyoma of the entire muscular wall of the lower third of the esophagus, extending into the outer wall of the cardiac fourth of the stomach.

The type of operation depends on whether the growth is submucous, pedunculated, intramural, or arises from the muscular coat of the esophagus. The pedunculated tumors may be more accessible; and if the tumor is small and has its origin high at the introitus, it may be removed through the mouth with a snare and cautery. Larger tumors of this type require cervical esophagotomy. The tumors may attain such huge size as to require trans-thoracic esophagotomy. This approach may

of the difficulty in determining the type or extent of the growth; and the decision must await operative exploration. If the intramural tumors involve only a segment of the esophageal wall, they may be removed by trans-thoracic and transpleural local excision of the tumor from the wall, which is then reconstructed (Figure 34-9). If the growth involves the entire esophageal wall, its removal will require trans-thoracic and transpleural resection of the esophagus and transdiaphragmatic

esophagogastric anastomosis (Figures 34-10, 34-11, and 34-12).
Irradiation has no place in the treatment of benign tumors of the esophagus.

DATA ON FOURTEEN CASES OF ESOPHAGEAL TUMORS

The following is a summary of fourteen cases of tumor of the esophagus in which I

Tumors of the Esophagus

originated at the introitus of the esophagus. Of the twelve intramural tumors, ten were benign leiomyomas and two were malignant leiomyosarcomas. Seven of the benign intramural tumors were in the lower third, two were in the mid-third, and one was in the upper third of the esophagus. Three of the benign tumors were single, completely encapsulated, circumscribed growths involving

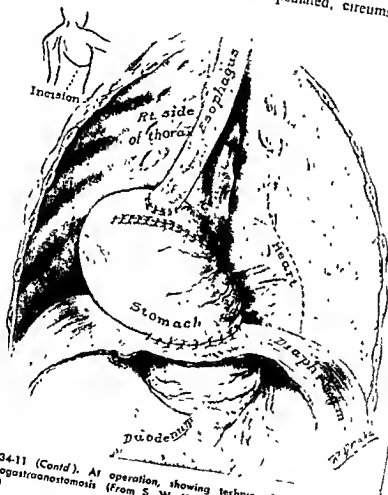


Fig. 34-11 (Contd.). At operation, showing technic of right transthoracic esophagogastric anastomosis (From S. W. Horrington [6], courtesy Archives of Surgery.)

have operated, eleven of which were previously reported [6, 7].

In the entire series of fourteen cases, two of the tumors were pedunculated and arose from the submucosa, and twelve were intramural. Two of these intramural growths had undergone malignant change and were leiomyosarcomas.

One of the two submucosal pedunculated benign tumors was a lipoma with a single pedicle, and the other consisted of two large fibromyomas with separate pedicles. Both

a relatively small segment of the outer esophageal wall; five were multiple leiomyomas of multicentric origin involving a large segment and from one to two thirds of the circumference of the wall of the esophagus; and the remaining two were a diffuse type of multiple leiomyoma involving the entire circumference of the outer wall of the lower part of the esophagus and a distance of from three inches to one third of the entire length of the esophagus. One of these growths extended into the cardia of the stomach.

Of the entire series of fourteen patients, six were women and eight were men. The youngest was nineteen and the oldest sixty years of age. The average age was forty-two years. The surgical procedure for the two pedunculated tumors was complete removal of the tumor following esophagotomy, one through a left cervical approach and one through a right transthoracic approach. Both patients re-

symptoms. In the remaining two of the ten cases of benign leiomyoma, the tumor involved the entire muscle wall of the lower part of the esophagus, one involving the cardia of the stomach as well. These two tumors were completely removed by transpleural and transdiaphragmatic resection of the lower part of the esophagus and the cardinal end of the stomach, with esophagogastrastomosis.



Fig 3-12. Same case as figures 3-10 and 3-11. a One year after operation. Half of the stomach is above the diaphragm. The esophagitis was patent, and there were no symptoms. b. Surgical specimen. Diffuse leiomyoma measuring 8 X 5 X 3 cm.

covered from operation and have been relieved of symptoms. Seven of the ten benign intramural leiomyomas were completely removed by excision of the tumor followed by reconstruction of the muscle wall of the esophagus, and only the abdominal portion of one tumor was removed. The approach for the removal of these eight tumors was right transpleural in four cases, and left abdominal in one case. All eight patients recovered from the operation and have been relieved of

The approach for one was through the right thoracic cavity and for the other through the left thoracic cavity. One of these patients died on the fourth postoperative day from bilateral pneumonia; the other recovered from the operation and has been completely relieved of symptoms. The two patients with malignant leiomyosarcomas were operated on through a left posterolateral approach. In one case the tumor was found to be inoperable because of extension into the pericardium, aorta, and mediast-

tinal structures. The other leiomyosarcoma was completely removed along with the lower half of the esophagus and the cardial end of the stomach, and a transdiaphragmatic esophagogastric anastomosis was done. This patient recovered from operation and has had relief of symptoms and no recurrence of the tumor for five years following the operation.

In summarizing the results in the series of fourteen cases, it may be said that one patient died following operation, one had an inoperable malignant neoplasm, and twelve recovered from operation and have been relieved of symptoms for periods varying from ten months to eleven years after operation.

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Surgical Management of Malignant Tumors of the Esophagus

Richard H. Sweet

Intelligent surgical treatment of malignant esophageal tumors must be based upon an understanding of the biologic characteristics of the neoplasms. *Epidermoid carcinoma* is the growth most frequently encountered. Although it bears some histologic similarities to the relatively benign carcinomas of the skin that grow slowly and metastasize late, carcinoma of the esophagus is a highly malignant tumor, comparable in the degree of malignancy to epidermoid carcinoma of the anal canal. By the time patients suffering from this cancer reach the operating table, the growth has in a large number of instances already infiltrated the muscular wall of the esophagus. Likewise, in cases amenable to surgical extirpation, 52.5 per cent of these tumors have already metastasized to the regional lymph nodes. Thus, even in the majority of patients whose growth can be removed, the possibility of cure is already seriously compromised by the time the patient reaches the surgeon. The operative procedure should therefore include the most extensive possible extirpation of the tissues that are likely to be involved in the spread of the cancer.

A certain proportion of carcinomas in the lower end of the esophagus are *adenocarcinomas*. The majority of these are actually gastric in origin, arising from the mucous membrane of the stomach at the cardia. It is probable also that the intrinsic mucous glands of the esophageal mucosa may become the site of malignant neoplasia in some instances, but the differentiation of these from tumors arising from gastric mucous membrane is difficult and of no practical importance.

Malignant tumors of the esophagus other

than carcinoma occur infrequently. Two types that arise from muscle cells may be encountered. *Leiomyosarcomas* of smooth muscle fiber origin may develop at any level within the esophagus. In the upper end, sometimes as far down as the superior mediastinal segment, where there may be a few striated muscle fibers, an occasional case of *rhabdomyosarcoma* may be seen. Tumors of the sarcoma group tend to infiltrate, and local recurrence is frequent.

In a few instances at the lower end of the esophagus a peculiar form of malignant neoplasm involving two types of epithelial cells is encountered. It is usually designated *adenacanthoma*. Though rare, it occurs more frequently than tumors of the sarcoma group.

Another rare type of growth occasionally encountered consists of a combination of cells arising from both the epithelial and the muscular layers. It is spoken of as a *carcinosarcoma*.

Lymphoma of the esophagus is sometimes observed. It is usually discovered only after extirpation of what was thought to be a carcinoma. If there is a generalized lymphoma with lymph node involvement, the diagnosis can be made by lymph node biopsy and the patient thereby spared the ordeal of a major operation because of the usual susceptibility of these tumors to the effects of roentgen irradiation.

PROBLEMS OF SURGICAL EXCISION

The technical problem involved, insofar as the esophagus is concerned, has to do with the regional lymph nodes which may be the site of metastases and the topographic rela-

tions of the esophagus itself.

Considering the esophagus as a whole, there are six important groups of lymph nodes to which metastases may spread. These are as follows (Figure 35-1): (1) the *cervical group*, comprising all the deep lymph nodes of both sides of the neck; (2) the *superior mediastinal group*, which lies in relation to the trachea, the esophagus in that region, and the great

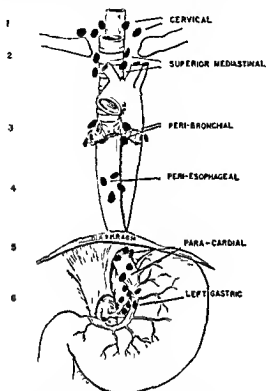


Fig. 35-1. Diagram of the principal groups of lymph nodes that may become invaded by metastases from carcinoma of the esophagus.

vessels (paravascular nodes); (3) the *subcarinal and peribronchial groups*, which lie in relation to the major bronchi of both lungs; (4) the *periesophageal nodes of the lower mediastinum*, which communicate with the nodes in the pulmonary ligaments; (5) the *paracardial group*, which consists of a ring of nodes encircling the gastric cardia and the abdominal segment of the esophagus; (6) the *left gastric group*, a large and important cluster of nodes that is found along the proximal portion of the lesser curvature of the stomach and around the origin and branches of the left gastric artery.

Obviously, it is impossible to remove all these groups of regional lymph nodes in any

one case of carcinoma of the esophagus. It is apparent also that the extent of regional node excision possible in any case depends upon the region in which the primary growth lies. In general, the direction of lymph node drainage, as manifested by the greatest frequency of metastases to the various anatomic groups, appears to be downward. Thus, in carcinoma of the cervical segment, although the nodes in both sides of the neck are frequently involved, those in the superior mediastinum are often likewise invaded. When the superior mediastinal segment of the esophagus is the site of the primary tumor, not only are the nodes in that portion of the mediastinum frequently invaded but also those in the peribronchial and subcarinal regions, and often even those in the lower mediastinum or upper abdomen. From this point downward, the nearer the growth lies to the diaphragm, the greater is the tendency for the lower mediastinal, the paracardial, and the left gastric groups of nodes to be involved in metastases. In fact, the latter two groups of nodes are involved in over 70 per cent of all those cases of carcinoma of the thoracic portion of the esophagus, below the superior mediastinal segment, where proved metastases to lymph nodes are found.

With this knowledge of the behavior of metastases to lymph nodes and the peculiarities of the anatomic relation of the esophagus, the possibility of performing a completely satisfactory ablation of the cancerous tissues in a given case of carcinoma of the esophagus bears a direct relation to the location of the growth. Thus, it will be seen that in the cervical segment the confines of the region and the proximity of important structures such as the trachea, the recurrent laryngeal nerves, and the great vessels of the carotid sheaths preclude the removal of any large amount of periesophageal tissue. Furthermore, the necessity for preserving the blood supply to a flap of skin and platysma muscle that is to be employed to bridge the gap after the resection has been carried out prevents the performance of a wide bilateral cervical lymph node dissection. (For a discussion of the indications and technic of bilateral neck dissection, see Vol. III, Chap. 43.) In the neck, therefore, it is practically impossible to approach the

ideal radical extirpation necessary for a successful result from the point of view of cure. It should be pointed out that the curability of carcinoma in this segment cannot be improved by performing a total esophagectomy because of these same limitations imposed upon the possibility of effecting a thoroughly radical extirpation of the local cancer and the regional nodes.

In the superior mediastinum the situation is very similar to that when the growth lies in the cervical segment, because of the limited extent of local and regional dissection that can be carried out owing to the restrictions of the region involved.

From the superior mediastinum downward, however, the possibility of performing a reasonably satisfactory wide excision of the primary tumor along with an adequate number of regional lymph nodes increases. Although there is little opportunity to remove a large enough number of the nodes in the peribronchial and subcarinal regions, it is possible to excise a large number of the lower mediastinal nodes and practically all those in the paracardial and left gastric regions. This fact is reflected in the five-year survival rate of patients with carcinoma of the esophagus after radical resection.

CHOICE OF CASES FOR SURGICAL RESECTION

It is the responsibility of the surgeon to attempt a resection whenever there is a reasonable prospect that the growth can be removed. In the practice of this policy, approximately 85 per cent of patients can be explored and of those explored, 75 per cent have a resectable growth [10]. This includes all cases, whether probably curable or not. Thus, it is possible to perform a resection in 65 per cent of all patients seen.

In the 15 per cent of patients who should not be operated on, the contraindications include evidence of serious disease of the heart, lungs, kidneys or, more frequently, evidence of spread of the carcinoma, either by direct extension to vital contiguous structures (spine, tracheobronchial fistula) or metastases to distant organs (liver, etc.). Advanced age of a patient is not in itself a contraindication.

Of those who are explored without the accomplishment of a resection, the usual causes for inoperability are local fixation or invasion of vital structures such as the aorta, the trachea, bronchi, or the pericardium, or evidences of irremovable metastases to inaccessible nodes or the liver. On rare occasions the operation may have to be terminated because of deterioration of the patient's condition or, as in two instances, because of the presence of an area of localized arteriosclerotic weakening of the aorta or such fragility of the aortic wall that rupture might occur if it were pressed upon during the process of dissecting free an adherent carcinoma.

OPERATIVE TECHNIC

For the purpose of description, it is expedient to start with the procedure employed for the removal of carcinoma of the lower end of the esophagus and cardia. With a growth at this level, the operation can be made to approach the theoretically ideal cancer operation. It is then necessary merely to describe the modifications of the procedure that are required to deal with neoplasms in the various higher levels.

Operation for Carcinoma of the Lower Esophagus and Gastric Cardia: Proximal Partial Gastrectomy and Esophagectomy with Low Intra-thoracic Esophagogastric anastomosis

For a growth involving primarily the lower end of the esophagus and gastric cardia, a left standard thoracotomy incision, including the resection of the entire eighth rib, is employed [9]. The patient is placed on his right side with the arms forward and the knees bent to help maintain a stable position. The operating table should be angulated in the middle to produce a lateral bend of the patient, which arches the left hemithorax upward in order to spread the ribs slightly. The skin incision should extend from the left costal border along the course of the eighth rib to the angle, whence it should curve upward for a short distance. As soon as the skin is divided, towels are attached to each edge to cover all but the actual field of operation.

The muscles that must be divided are the latissimus dorsi, the lowermost portion of the

trapezius, the serratus anterior, and a portion of the erector spinae muscle posteriorly. The eighth rib costal attachments of the external oblique muscles are parted anteriorly. The eighth rib is resected, cutting it in front through its cartilaginous segment and in back through its neck (Figure 35-2). The periosteum and pleura are incised and with the wound edges well protected by large pads of gauze, a rib spreader is inserted to gain an adequate exposure.

For carcinoma near the cardia, it is rarely necessary to enlarge the incision either in front (by cutting the costal cartilage) or in back (by dividing the superjacent ribs) [9].

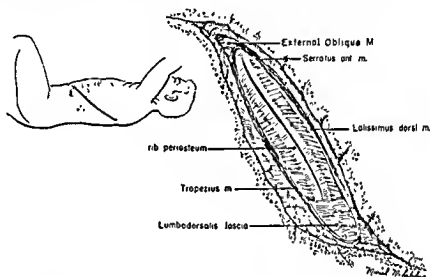


Fig. 35-2. Incision employed for partial proximal gastrectomy and esophagectomy for carcinoma of the lower end of the esophagus. (From Nelson Loate-Leaf Surgery [8].)

If the left lung is adherent to the parietal pleura and diaphragm, an extensive dissection must be carried out to free it sufficiently to expose the entire diaphragm and the mediastinal pleural reflection from the level of the aortic arch down.

The esophagus is exposed through a longitudinal incision in the pleura anterior to the descending aorta a few inches above the diaphragm. After the esophagus has been freed by blunt dissection above the level of the tumor, a strip of Penrose drain (rubber) is passed around it to aid in retraction. The growth is then explored to decide whether or not it can be removed (Figure 35-3). If excision appears to be feasible, the phrenic nerve is crushed at the point where it leaves the

pericardium and a short incision is made through the muscular portion of the diaphragm in the direction of its fibers. Exploration of the upper abdomen through this preliminary incision will detect the presence or absence of metastases to the liver or the lymph nodes in the paracardial and left gastric artery regions. If no reason for abandoning the operation is found, the diaphragmatic incision is enlarged by extending it through the margin of the esophageal hiatus. Close to the margin of the hiatus one should find the arch of the left inferior phrenic artery for ligation and division. The incision thus completed gives a wide exposure of the left sub-

diaphragmatic region and the lower half of the left thoracic cavity.

The dissection is begun by freeing the lower esophagus, starting at a level several inches above the growth. One or two esophageal branches of the aorta must be divided and tied, along with several small vessels, both arteries and veins, which enter into the collateral circulation in this region. As the lower segment of the esophagus is mobilized, the periesophageal group of lymph nodes must be freed and left attached to the portion which is to be excised. As the dissection is carried downward into the upper abdomen, the attachments within the esophageal hiatus of the diaphragm and the peritoneal reflections from the superior pole of the spleen, the fundus of

the stomach, and the gastrohepatic ligament must be severed. At this level, branches of the inferior phrenic, superior suprarenal, and ascending trunks from the left gastric arteries must be divided. In a large percentage of patients an anomalous artery is found in the subdiaphragmatic portion of the gastrohepatic ligament, extending from the upper branches of the left gastric artery to the porta of the liver. This vessel must be severed. In certain instances the growth or its metastases in the

is encountered. With the division of this vessel the only remaining attachments of the upper portion of the stomach are those around the left gastric vessels, including the lymphatic communications with the channels around the celiac axis and the termination of the right vagus nerve which frequently can be identified in this region as a large single trunk. These tissues and the left gastric artery and vein are severed between long hemostatic forceps and ligated. The division of the left gastric artery

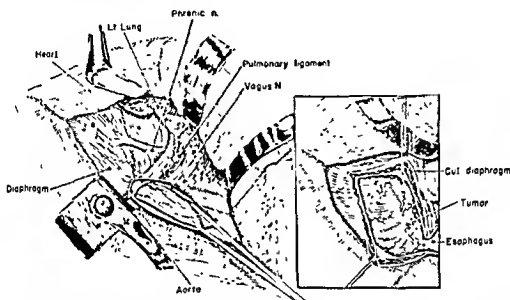


Fig. 35-3. Exposure of the lower esophagus for exploration through a linear incision in the mediastinal pleural reflection anterior to the descending aorta (Inset) Exposure of the cardia and proximal portion of the stomach by incision of the diaphragm (From Nelson *Textbook of Surgery* [8].)

paracardial lymph nodes may be so adherent to the margins of the esophageal hiatus that a rim of diaphragm should be excised along with the attached tumor mass.

After the liberation of the lower esophagus has been accomplished, the upper portion of the stomach must be freed (Figure 35-4). This part of the dissection is begun in the gastrocolic ligament where, in an avascular region, a small opening is made with scissors into the lesser omental bursa. Division of the attachments of the stomach along the greater curvature at this level involves cutting the left gastroepiploic vessels and the vasa brevia, thus freeing the stomach from the spleen. As this is accomplished, an isolated branch of the splenic artery that enters the posterior surface of the fundus of the stomach

is made as close as possible to its origin from the celiac axis in order to remove all the lymph nodes which lie in relation to the branches of the artery as they approach the lesser curvature of the stomach. Unfortunately, it will be observed in some patients that the metastatic lymph node involvement in this region is not confined to the left gastric group but has actually extended to communicating nodes around the celiac axis and along the abdominal aorta or behind the pancreas. Obviously, these nodes cannot be removed and the most that can be expected under the circumstances is to provide palliation without hope of cure.

Although the lower esophagus and proximal half of the stomach have been completely mobilized as a result of the dissection thus far

described, it is important to extend the division of the gastrocolic ligament distally almost to the level of the pylorus. In doing this, the integrity of the anastomotic arcade of vessels along the greater curvature must be preserved, but the omental branches of the gastroepiploic vessels are, of course, divided. This division of the gastrocolic omentum is carried out in all cases, not only to provide the necessary mobility of the stomach required, particularly

Tumors of the Esophagus

of this part of the operation vary slightly, depending upon whether an end-to-side or an end-to-end esophagogastric anastomosis is to be used. In the majority of instances, particularly with carcinoma primary in the esophagus as opposed to one arising in the cardiac end of the stomach, an end-to-side approximation can be employed. If allowances are made for certain important technical details upon which the success of the procedure depends,

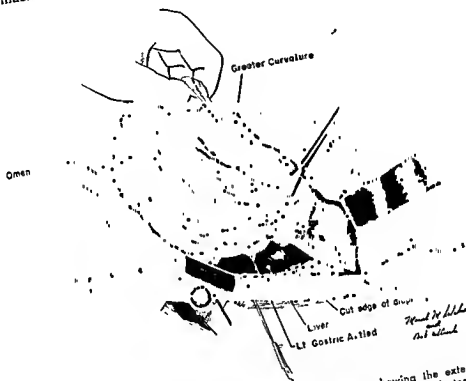


Fig 35-4 Carcinoma of the cardia and lower esophagus; showing the extent of mobilization of the stomach and esophagus required to perform a satisfactory resection. The left gastric and left gastroepiploic arteries and the vasa brevia have been divided and tied. (From Nelson Loose-Leaf Surgery [8].)

when a high intrathoracic anastomosis is to be made, but also to divide as many sympathetic nerve fibers as possible in the hope that this maneuver may ameliorate the tendency to pylorospasm induced by dividing both vagus nerves. It should be emphasized that in order to maintain an adequate blood supply to the stomach, both the right gastric and the right gastroepiploic arteries must be preserved.

The next step in the procedure consists of the excision of the diseased segment and the performance of an anastomosis to restore the continuity of the alimentary canal. The details

this method is safer in the hands of the average surgeon than the end-to-end method, which necessitates the employment of suture lines that come together at right angles, leaving a potentially weak point where leakage might occur unless great care and skill are employed.

END-TO-SIDE ANASTOMOSIS

Upon completing the mobilization of the lower end of the esophagus and the stomach, protection of the field of operation is provided by inserting over each wound edge a pad of gauze moistened in warm saline solution. The

stomach is held with the greater curvature and fundus uppermost and the site of transection is prepared by dividing the vessels at appropriate levels on each curvature. On the greater curvature a long portion of normal stomach can be preserved. On the lesser curvature, however, the site of transection must be several inches below the cardia at a point where the vessels can be severed distal to the group of lymph nodes that must be removed.

Kocher variety. Of these, the latter is preferable because the curvature of the blades makes it possible to save more of the stomach than when the straight Payr clamp is used. The other style, known as a Seudder clamp, has long, curved or straight, fenestrated blades through which a suture can be passed. If only a crushing clamp is available, two such clamps are applied and the stomach is cut close to the distal clamp with a knife (Figure 35-5).

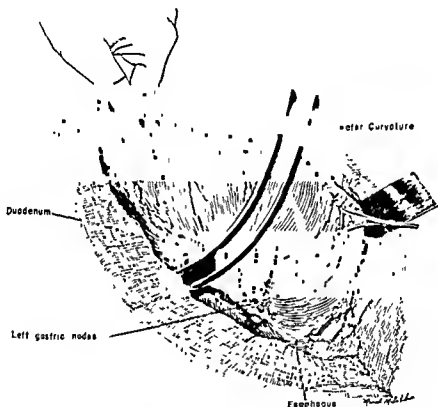


Fig. 35-5. Position of clamps on the stomach, showing the direction of transection necessary to remove the left gastric group of lymph nodes along the lesser curvature. (From Nelson *Loose-Leaf Surgery* [8])

The division of the vessels must be made, therefore, through the descending branches of the left gastric artery or even in some instances through the anastomotic branches of the right gastric artery. Thus, the direction of the transection of the stomach must be oblique, leaving a short distal portion of the lesser curvature and preserving a long portion of the greater curvature.

After the vessels along the curvatures have been divided, a long gastric clamp is applied at the level chosen for division. Two types of clamp are available for this purpose. One is a crushing clamp such as the Payr or the

A strand of 00 catgut provided with a straight atraumatic needle is then employed to suture the stomach wall by passing the needle back and forth from one curvature to the other beneath the blades of the clamp. The clamp is then removed and the edges of the stomach wall thus freed are sutured over and over back to the starting point, using the same suture and needle (Figure 35-7A). This maneuver serves to prevent spilling of gastric contents and tends to prevent bleeding from the severed intramural vessels. The objection to the crushing clamp, however, is that hemorrhage into the stomach may result from the mucous

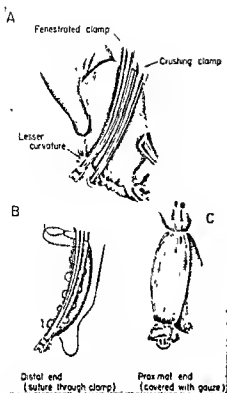


Fig. 35-6. Details of division and closure of the stomach. (From R. H. Sweet [9], courtesy W. B. Saunders Company.)

membrane edges that are sometimes actually cut by the action of the clamp and may then retract beneath the jaws of the clamp beyond reach of the suture.

The use of a fenestrated clamp provides a more certain means of preventing hemorrhage of the edges of the stomach wall. This clamp is applied at the proper level in the usual manner. The proximal clamp (crushing) is applied next and the stomach is cut between. The continuous suture is then begun, this time passing it through and through the blades of the clamp instead of beneath them (Figure 35-6B). After the fenestrated clamp has been removed, the suture is carried over and over the edge back to the starting point as described above (Figure 35-7A).

The closure of the stomach is completed with a continuous catgut suture to invert the divided and previously sutured edges. Further reinforcement is provided with an outer layer of Lembert sutures of silk (Figure 35-7B).

In order to diminish the degree of soiling of the operative field, the proximal end of the stomach is covered with a gauze pad tied over the clamp with a strand of heavy silk.

In preparation for the anastomosis, a circular incision of a diameter commensurate with that of the esophagus is made on the anterior wall of the stomach through its serous and muscular walls, avoiding injury to the intramural vessels (Figure 35-8). This incision should not be made too close to the inverted end of the stomach because of the danger of interrupting the blood supply to the portion of gastric wall that lies between. Furthermore, although it is usually placed near the greater curvature, it should not interrupt any important branch of the gastroepiploic vessels. Before the anastomosis is started, a series of suture ligatures of fine silk (00000) is applied to the small intramural vessels that cross the region outlined by the circular incision. The final excision of this circular portion of the gastric wall is delayed until after the first two of the three layers of the posterior aspect of the anastomosis have been completed. This delay in the actual opening of the stomach makes it easier to start the anastomosis and diminishes the length of time when contamination from the open lumen may occur.

After the site of the anastomosis has been prepared on the wall of the stomach, the esophagus is cleared for division at a level

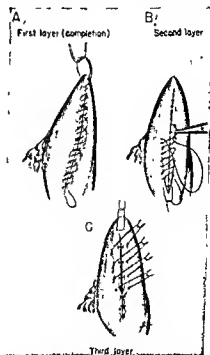


Fig. 35-7. Details of closure of the stomach. (From R. H. Sweet [9], courtesy W. B. Saunders Company.)

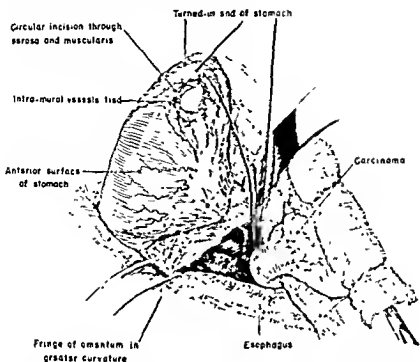


Fig. 35-8. Preparation of the site of anastomosis on the anterior surface of the gastric wall. First suture of the posterior aspect of the anastomosis placed but not tied. (From Nelson Loose Leaf Surgery [8].)

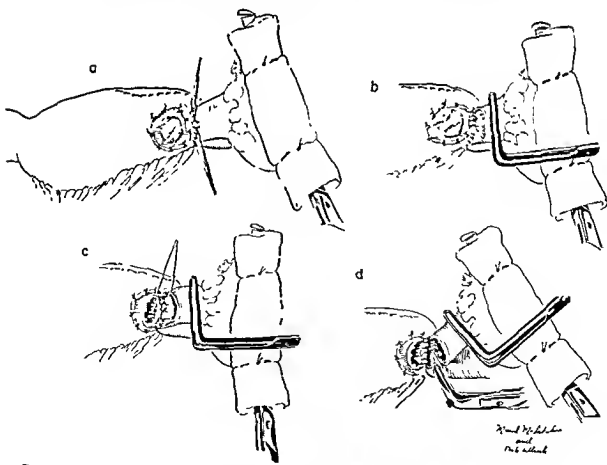


Fig. 35-9. Details of esophagogastric anastomosis; posterior aspect. (From Nelson Loose-Leaf Surgery [8].)

several inches proximal to the upper limits of the growth and well above the periesophageal group of lymph nodes in the lower mediastinum. This involves severing both vagus nerves, the proximal ends of which should be ligated in order to secure the small vessels that lie close to them. Any small longitudinal branches of the nearest esophageal artery above the intended site of transection are tied and cut. Several small veins must be divided as well.

The anastomosis is begun with a layer of mattress sutures of 00000 silk between

the stomach of its contents. The previously outlined circular portion of gastric wall is then excised, thus creating a round aperture for the anastomosis. The posterior portion of the esophageal mucosa is incised next and the posterior portion of the mucosal approximation is completed with interrupted sutures of fine silk (00000) or catgut, as desired (Figure 35-9). Using a pair of scissors with bent blades, the remainder of the circumference of the esophagus is severed and the tumor-bearing specimen is removed (Figure 35-9).

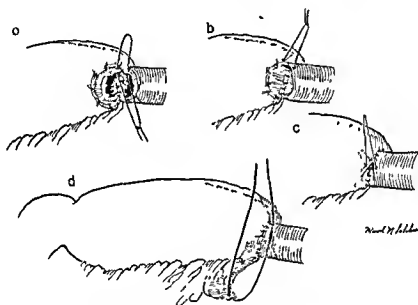


Fig 35-10. Details of esophagogastric anastomosis; completion. (From Nelson *Loose-Leaf Surgery* [8].)

the muscularis of the posterior surface of the esophagus and the seromuscular coats of the contiguous stomach wall (Figure 35-9). After enough sutures of this layer have been inserted to comprise approximately one third of the circumference of the anastomosis, a right-angled clamp is applied to the esophagus about one inch distal to the level of division and the muscle layer of the esophagus is divided down to the mucosa. A second row of sutures approximating the cut edges of the muscularis of both organs is applied (Figure 35-9).

A small opening is now made through the mucosa of the stomach at any convenient point in the line of the circular seromuscular incision and an aspirator is inserted to empty

The anastomosis is completed by continuing the posterior layers around the circumference anteriorly in reverse order, starting with the mucous membrane layer and finishing with the outer layer of mattress sutures used to approximate the muscularis of the esophagus and the serosa of the stomach. The sutures in the mucosal layer are inserted so that the knots, when tied, lie within the lumen. On its completion the anastomosis is exactly circular (Figure 35-10).

END-TO-END ANASTOMOSIS

Whenever it becomes necessary to remove so large a portion of the stomach that it is impossible to employ an end-to-side approximation because of excessive tension on the

suture line, it is preferable to use an end-to-end anastomosis. The technic of this method consists of a modification of that used for the end-to-side anastomosis. A long clamp is applied in an oblique direction across the stomach, preserving as much length along the greater curvature as possible. Near the greater curvature end of the portion of the stomach that lies distal to the clamp, a short, straight clamp (Ochsner) is put on at right angles to the greater curvature to avoid the creation of

35-11). The crushed edges of the portion of stomach held by the short clamp are excised to provide untraumatized tissues for the anastomosis.

Tension on the anastomosis is prevented by attaching the stomach to the edge of pleura along the mediastinal incision by a series of sutures of fine silk. The cut edges of the diaphragm are sutured to the stomach at an appropriate level, but caution must be exerted to avoid the constriction of the stomach that

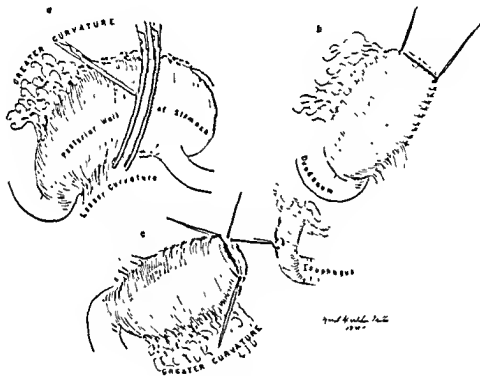


Fig. 35-11. Details of alternate method of esophagogastric anastomosis by the end-to-end method.

a sharp angle at the end of the gastric remnant (Figure 35-11). The stomach is divided by cutting along the edges of these clamps with a knife. The portion that is held by the longer clamp is closed in exactly the same manner as in the end-to-side method, leaving the portion held by the smaller clamp for the anastomosis. Two layers of catgut with an outer layer of silk are employed (Figure 35-11). The anastomosis between the esophagus and the opening that remains after the partial closure of the distal portion of the stomach is accomplished with three layers of 00000 silk sutures in the same manner as described previously for the end-to-side technic (Figure

would result from making the diaphragmatic closure too tight (Figure 35-12). The remainder of the diaphragmatic incision is then closed, using interrupted sutures of heavy silk.

Operation for Carcinoma of the Mid-Thoracic Segment of the Esophagus: Partial Esophagectomy with High In-thoracic Esophagogastric anastomosis

There is no widespread uniformity of opinion among surgeons interested in the technical problems involved in the removal of carcinoma in the mid-thoracic segment of the esophagus. It is possible, however, to present certain

principles that should be considered. With the twofold objective in mind that the operation must include the widest possible extirpation of the growth with the regional lymph nodes and also provide a successful restoration of continuity of the alimentary canal, there are two avenues of approach that can be employed, namely, a left thoracic or thoraco-abdominal incision, with performance of the anastomosis above and in front of the aortic arch, and a combined left laparotomy and

double-incision procedure. There is the further advantage that with this incision the resectability of the growth can be determined immediately, whereas with the alternative method the surgeon may subject the patient to a rather long and difficult abdominal operation only to find on opening the right side of the chest that the growth cannot be removed.

With few exceptions the technique of the operation for removal of a growth in the mid-esophagus using the left thoracotomy

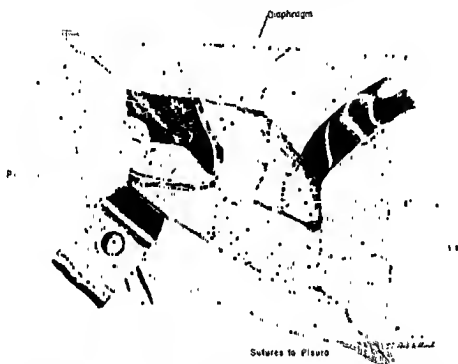


Fig. 35-12. Closure of the diaphragm around the stomach after completion of the anastomosis. (From Nelson Loose Leaf Surgery [8].)

right thoracotomy, involving usually the use of two separate incisions.

THE SINGLE INCISION, LEFT THORACIC APPROACH

The advantages of performing the operation through a standard thoracotomy incision on the left side are principally (1) that only one incision is required, (2) that the position of the patient on the table is maintained without the necessity of shifting from back to side, (3) that the extensive mobilization of the stomach required for the performance of a high anastomosis can be more easily accomplished, and (4) that because of the above, the operating time is shorter than with the

approach is identical with that already described. The incision, however, should be made slightly higher and should include resection of the seventh rib instead of the eighth. In the majority of patients this level is low enough to provide ready access to the stomach, although in those whose chest is short and unusually broad, with a more nearly transverse inclination of the ribs, it may be preferable to resect the eighth rib. Furthermore, in many such patients no upward enlargement of the incision is required. With regard to the degree of exposure of the esophagus in the region above the aortic arch, where the anastomosis is to be made, variations of the build and topography of the patient's

the lower end, the esophageal aortic branches, branches from the bronchial and intercostal arteries, and occasionally one or two from the inferior surface of the aortic arch. Once all these have been divided, the only blood supply remaining consists of descending branches from the inferior thyroid arteries and occasionally an anomalous branch from the subclavian or highest intercostal arteries. It is important, therefore, whenever the high level of the growth requires a dissection extending behind or above the aortic arch, to place the level of transection of the esophagus above the arch in order to be certain of the viability of the proximal end that must be employed for the anastomosis.

In some patients, as the portion of the esophagus which lies behind the aortic arch is being freed, there may be considerable disturbance of the cardiac rhythm or a sharp fall in the systemic blood pressure. A few moments of interruption of the dissection, accompanied by full inflation of the lung to improve the degree of oxygenation, usually suffice to correct the difficulty and the operation can be resumed.

Sometimes if it is difficult to free an adherent growth located behind the aortic arch, this step of the procedure can be accomplished by dividing the upper one or two left intercostal arteries so that the aorta can be retracted forward.

Just above the level of the aortic arch the thoracic duct is usually encountered as it crosses to the left of the esophagus in its ascent into the neck. If the duct is adherent to the growth, a segment must be excised. Sometimes it may be injured in the dissection, even though not invaded by tumor. In either event the ends should be ligated in order to prevent subsequent leakage of chyle.

After the dissection of the esophagus has been completed, the diaphragm is incised completely and the stomach is mobilized extensively, preserving the right gastric and right gastroepiploic arteries with their anastomotic arcades along the lesser and greater curvatures. In order to accomplish the preservation of the arcade upon the lesser curvature, the left gastric artery must be tied close to its origin, thus maintaining a flow of blood from the right gastric artery by way of intercom-

munications between its branches and the descending branches of the left gastric, which in turn pass the flow upward through the remainder of the large trunk of this vessel and its ascending branches to the region of the cardia (Figure 35-13, *inset*).

In order to have a sufficient length of stomach for the performance of an anastomosis at a high level, above the arch of the aorta, the entire fundus must be preserved with an adequate blood supply. This involves a compromise on the theoretically ideal resection from the point of view of radical removal of possible cancer-bearing tissues because of avoiding interruption of the continuity of vessels along the lesser curvature. In this instance, therefore, the lymph nodes that lie in relation to the branches of the left gastric artery along the lesser curvature cannot be removed because the stomach must be divided close to the cardiac orifice. The paracardial nodes, however, can usually be excised and consolation may be had from the knowledge that the higher the level of the growth in the esophagus, the less is the likelihood of metastasis to the left gastric nodes.

The transected stomach is closed and inverted in the same manner as described previously, using this time a straight clamp with short, fenestrated blades. A rubber glove or square piece of rubber tissue is tied over the proximal cut end of the esophagus. The esophagus is then pulled up from behind the aortic arch and the stomach is drawn up into the apex of the chest for the performance of the anastomosis (Figure 35-14). The circular incision of the gastric wall is made close to the apex of the fundus in order to take full advantage of the length obtained by preserving this portion of the stomach. The technical details of the anastomosis are exactly the same as in cases requiring an anastomosis low in the chest, but unusually long instruments should be employed.

Upon completing the three-layer anastomosis, a few sutures of silk are placed on either side between the fundus and the adjacent edges of the mediastinal pleura above the aortic arch. Further support of the stomach for the relief of tension on the anastomosis is secured by means of a row of sutures to the pleura overlying the descending aorta.

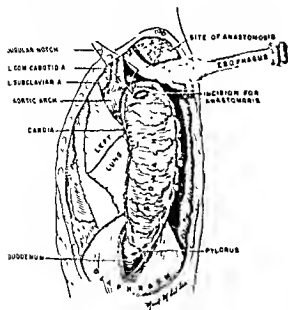


Fig. 35-14 Start of high intrathoracic esophagogastric anastomosis. (From Nelson *Textbook of Surgery* [8])

The diaphragmatic closure in cases requiring a high-level anastomosis embraces the stomach a few centimeters above the pylorus.

THE COMBINED ABDOMINAL, RIGHT THORACIC APPROACH

This subject is discussed in Chapter 36.

Operation for Carcinoma of the Superior Mediastinal Segment: Subtotal Esophagectomy with Intracervical Esophagogastric Anastomosis

Fortunately for both the patient and the surgeon, carcinoma arises in the superior segment of the esophagus less frequently than in any other portion. The technical problem presented by a growth in this region in itself usually taxes the ingenuity and skill of the surgeon, but of even more importance is the relative impossibility in these cases of accomplishing a satisfactory removal of the growth and the regional lymph nodes. The narrow confines of the region involved and of the contiguous region in the base of the neck, together with the close proximity of vital blood vessels, important nerves, the trachea, and the thoracic duct, which must not be injured, make dissection difficult and removal impossible excepting in early and relatively favorable cases. A growth in this location extends too low for the use of the

Wookey operation (Vol. III, Chap. 15), which requires the employment of a flap of skin and platysma muscle from the neck, and it lies too high to make it possible to perform an anastomosis with the stomach in the apex of the chest. The only satisfactory surgical approach thus far available consists in some modification of the procedure employed for the extirpation of a growth in the mid-thoracic segment. Although it is possible almost without exception to bring the fundus of the completely mobilized stomach into the neck for the performance of an anastomosis with the esophagus or even with the hypopharynx, it is necessary, in order to accomplish the desired result, to add to the procedure a separate cervical incision.

As with carcinoma of the mid-thoracic segment of the esophagus, the procedure can be carried out either through a single left thoracic incision with an additional left cervical incision for the anastomosis or by a combination of a left abdominal and right thoracic incision with the placement of the cervical incision in the right side of the neck. Not enough collective experience with these methods is yet available to determine with certainty which is preferable, but on the basis of a comparison of the results of a limited trial of each, it appears that a single left thoracic incision plus a left cervical incision is preferable to the more complicated triple-incision technic involving the use of the abdomen and right thorax separately. This impression is fortified by the report of Nuboer [3]. This method makes it possible to determine whether or not the growth can be removed early in the procedure; it requires two incisions instead of three, and appears to be less frequently attended by serious complications involving the respiratory organs than the technic involving the right side, which requires three incisions.

SINGLE LEFT THORACOTOMY WITH LEFT CERVICAL INCISION

The left thoracotomy incision is made in exactly the same manner as for carcinoma of the mid-thoracic region. The double-rib resection method previously described should be employed in suitable cases. By resecting the upper rib first, the region of the tumor can be explored as soon as the chest is opened

and the operation can be terminated promptly if conditions are unfavorable for resection. If the growth can be dissected free from its surroundings, the entire thoracic esophagus and stomach are mobilized as described above. The stomach is transected at the cardia and the divided end is inverted. A rubber glove is tied over the cut end of the esophagus. A strand of silk is attached to the apex of the fundus to be placed in the base of the neck after drawing the lower portion of the esophagus up from behind the aortic arch. The stomach may be passed up the mediastinum behind the aortic arch and thus into the neck through the bed of the esophagus, or it may be drawn up in front of and lateral to the arch and thence into the neck. With the fundus held high within the chest, the lower half of the stomach is attached to the pleura over the descending aorta and the diaphragm is closed around the prepyloric portion. The drainage catheter is then inserted, the lung is expanded, and the chest incision is closed.

To complete the operation, which must of course be done in one stage, the patient is rolled onto his back. After suitable preparation of the skin of the neck and the application of fresh, sterile drapes, an incision is made along the anterior border of the left sternocleidomastoid muscle from the jugular notch to a point approximately two thirds of the distance to the angle of the jaw. The omohyoid muscle is divided and the sternal attachments of the sternohyoid and sternothyroid muscles are severed. The deep fascial layer is pierced and the esophagus is exposed. It is usually necessary to carry the freeing of the cervical esophagus slightly higher in the neck than was possible from within the chest during the thoracic phase of the operation. In doing this, however, the arterial branches supplying the segment must be preserved as intact as possible. When this mobilization of the cervical segment is completed, the esophagus above the growth is hooked with the finger and the entire organ is withdrawn from the mediastinum through the cervical incision. This maneuver is carried out in exactly the same manner as the withdrawal of the esophagus into the neck in the older Torek operation (see Chap. 37).

To bring the fundus into the neck for the

performance of an anastomosis with the esophagus above the growth, the previously attached strand of silk intended for identification is sought and, using this as a guide, the fundus is grasped with a Collin forceps and manipulated through the superior strait of the thorax into the neck. The anastomosis is then made in the customary manner, although it may be more convenient (because of the narrow space available) to use a linear incision in the gastric wall instead of excising a circular portion. The functional result of an anastomosis made in either way is equally good. With the completion of the anastomosis, the apex of the fundus is suspended in the neck by means of sutures to any available structure, including the thyroid and the fascia of the carotid sheath and the pretracheal muscles. The cervical incision is closed without drainage.

RIGHT CERVICAL, LEFT ABDOMINAL, AND RIGHT THORACIC INCISIONS

If the surgeon chooses to perform the mobilization of the stomach and thoracic esophagus through separate incisions, it is essential for him to satisfy himself as to the removability of the growth before subjecting the patient to the trauma of both a laparotomy and a thoracotomy without knowledge of the condition of the tumor itself. This can be accomplished by starting the operation with an exploration of the tumor-bearing segment through an incision in the right side of the neck made in the same manner as that just described on the left side. Through this it is possible to determine by palpation with the finger whether or not the growth is too adherent for removal.

If the growth is easily freed, temporary closure of the cervical incision is made and the operation is begun with a left abdominal incision followed by a right thoracotomy as already described. Upon completion of the mobilization of the esophagus during the thoracic phase of the three-phase operation, the stomach is severed and closed over, sutured within the chest, leaving the fundus free, and the chest wall is closed with catheter drainage in the usual manner. After the chest closure is completed, the neck is re-draped, the temporarily closed cervical in-

cision is re-opened, and the anastomosis is made within the neck as described on the left.

Reports from various surgeons are accumulating to confirm the opinion, based upon experience, that the postoperative course after the three-phase operation is much more tempestuous than that of the two-phase procedure. The most serious difficulties encountered have been a tendency to cardiac arrhythmia and pulmonary edema and, more important, acute laryngeal edema, vocal cord paralysis, a tendency to regurgitation and aspiration of gastric contents, and great difficulty with deglutition, which appears to be of a functional nature rather than a mechanical delay in the downward passage of material swallowed. Much less difficulty of this sort has been encountered when the two-phase, left-side operation has been employed, especially when the opening into the neck has been made large by resecting the inner end of the left clavicle and first rib as in the earliest cases where the procedure was employed [6].

The fact remains that an entirely satisfactory method of dealing surgically with carcinoma in the superior mediastinal segment of the esophagus has not yet been evolved.

Operations for Carcinoma of the Cervical Segment of the Esophagus

The method of segmental resection with restoration of continuity by substitution of a flap consisting of skin and platysma muscle from which a tubular graft is constructed, as devised by Wookey, is described elsewhere (see Vol. III, Chap. 15).

Short reference need be made to the suggestion occasionally advanced that a better way to handle carcinoma in the cervical segment is by an elaboration of the methods employed for the removal of a growth in the superior mediastinal segment. This suggestion is open to the following objections: (1) It is not possible to include a wide dissection of regional nodes or even a radical extirpation of the primary growth itself; (2) the operation carries a disproportionately high mortality; and (3) the functional result from the point of view of disturbances of laryngeal action, deglutition, etc. is not even remotely comparable to the excellent results obtained by the much safer and more simply accomplished

Wookey technic. The only drawback of the Wookey operation lies in the unfortunate fact that lymph node metastases are encountered frequently because of the extraordinary malignancy of the neoplasm and the failure in many instances to establish the diagnosis in an early phase of its evolution.

CARE OF THE PATIENT

Although there are still slight differences in unimportant details, the best methods of preoperative and postoperative care of the patient are now so well understood and so nearly uniform from one surgeon to another that it would be redundant to elaborate upon these matters at this point. They are described in adequate detail in Volume I, Chapters 9 and 10. A few remarks are appropriate, however, regarding the special problems of the immediate and late recovery periods of patients who have experienced an esophagectomy with esophagogastric anastomosis.

Immediate Recovery Period

ADMINISTRATION OF ANTIBIOTICS

If no technical faults such as an incompetent anastomotic suture have been allowed to intervene, the prophylactic administration of penicillin and streptomycin can be relied upon to eliminate the hazard of infection. Since these agents have been employed, no case of pleural, peritoneal, or mediastinal sepsis has been observed. The preoperative medication consists of parenteral injections of penicillin during the 24 hours preceding operation and the oral ingestion of a solution of streptomycin (0.25 Gm. per 100 cc. every 6 hours) during the two days preceding operation.

At the completion of the anastomosis, just before the diaphragm is closed, 30 cc. of a solution containing 100,000 units of penicillin and 1 Gm. of streptomycin are instilled, one half in the upper abdomen and one half in the mediastinum and pleural cavity. The administration of these antibiotics is continued by intramuscular injection during the first five days after the operation or until any suspicion of infection, including pneumonia, is over. A satisfactory dosage is 100,000 units of penicillin and 0.25 Gm. of streptomycin every six hours. If a pulmonary infection

should develop, the dosage and frequency of administration are adjusted to suit the exigencies of the occasion.

ADMINISTRATION OF OXYGEN

Although prolonged administration of oxygen after the completion of the operation is not necessary excepting in the presence of pulmonary or cardiac complications, it is wise to make use of this supportive measure during the first 24 hours, after which it can be discontinued in the usual case. The intranasal catheter method is the most satisfactory. In patients who have had an unusually high intrathoracic anastomosis, and especially those requiring a cervical incision with anastomosis at that level, it is often necessary to continue the administration of oxygen as long as four or five days. No routine can be established.

MAINTENANCE OF A CLEAR AIRWAY

In some patients, particularly those who have had a high anastomosis requiring the transposition of all or at least the greater portion of the stomach into the chest or through the chest into the neck, there may be considerable respiratory difficulty owing in part to temporary diminution of pulmonary volume and in part to difficulty on the part of the patient in raising secretions. Much of the trouble can be avoided by suitable prophylactic measures including the preoperative preparation with a low sodium intake and the avoidance of excessive intravenous administration of fluids, the avoidance of atropine, and occasionally the administration postoperatively of expectorants which the patient can swallow readily in a small volume of water, such as syrup of hydriodic acid.

When the accumulation of secretions in the trachea becomes excessive, repeated aspirations with a suitable catheter attached to a source of suction should be employed. Sometimes it is also difficult for patients to raise secretions from the pharynx without such assistance. If this method, which can be learned by the nurse, fails to reach the secretions that are causing difficulty, prompt resort must be made to bronchoscopic aspiration. This should be done without moving the patient from his bed and usually in the semirecumbent position because of the patient's

inability to assume a horizontal position.

In recalcitrant cases it may be necessary to resort to the performance of a tracheostomy so that frequent aspirations of the trachea may be carried out.

AVOIDANCE OF REGURGITATION FROM THE ESOPHAGUS AND STOMACH

In every case, a Levin tube should be inserted through the nose into the esophagus and adjusted so that its tip lies close to the level of the growth. If it is discovered during the operation that the tip of the tube has passed beyond the level of the growth, it should be withdrawn to the proper level by the anesthetist in response to the surgeon's directions as he palpates the tube through the wall of the esophagus. Constant suction on the outer end of the tube is maintained throughout the operation. In the cases of a low anastomosis, at the completion of this portion of the procedure the tube should lie with its tip in the lower esophagus just above the suture line. With patients who require a supra-aortic arch or an intracervical anastomosis, it is important to pass the tube through the anastomosis into the stomach. This is most easily accomplished at the time when the anastomosis is half completed and before the anterior aspect is begun. The necessity for draining the stomach in this manner during the first few postoperative days lies in the fact that regurgitation of gastric contents may occur so suddenly and in such large volume that the patient may aspirate large amounts of irritating liquid into the trachea or bronchi, sometimes with fatal result. This danger lasts only a few days, however, and it is usually safe to remove the tube on the fourth or fifth day after operation. In the low anastomosis cases, the danger of aspiration is minimal and the tube can usually be removed after twenty-four hours.

ASPIRATION OF THE PLEURAL CAVITY

At the completion of the operation, a large catheter is inserted through a lower intercostal space posterolaterally into the pleural cavity. A Foley urethral catheter is useful for this purpose because of the inflatable rubber bag near its tip which provides protection against its escape. After the patient has been re-

tured to his bed, the catheter is connected with a suction apparatus equipped with a valvular release to prevent the negative pressure within the system from exceeding the optimum level of 8 to 10 cm. of water. In the majority of patients the effusion of serosanguineous fluid has practically ceased by the end of forty-eight hours and the catheter can be removed.

CARDIAC REGIMEN

During the preliminary preparation of the patient, a low sodium diet is enjoined as one factor in the effort to reduce the possibility of developing pulmonary edema after operation. The intake of sodium is curtailed also during the first few postoperative days, but care must be exerted to avoid sodium depletion beyond a safe metabolic level. One dose of quinidine lactate is administered one hour before the anesthesia is begun to safeguard against the development of arrhythmias during the operative procedure. The administration of this drug is continued daily postoperatively until the danger of developing serious arrhythmias has passed, usually the fourth or fifth day. Digitalis is used if there is evidence of auricular fibrillation. In the majority of instances the patient should be given the benefit of the advice of a cardiologist regarding the details of administering these drugs.

EARLY AMBULATION

The majority of patients may be allowed out of bed on the second postoperative day. The brief time up should be utilized to walk to and fro in the room rather than merely to sit in a chair. In this way venous stagnation in the lower extremities may be diminished to some extent. In certain patients, however, particularly those who have had a high anastomosis, the degree of readjustment of the circulatory and respiratory functions necessary to allow this much activity is longer delayed. In these it may be wise to postpone rising from bed until the fourth or fifth day.

Late Recovery Period

Regarding the problems that confront the patient after he has left the hospital, the following quotation from a previous publication [7] is applicable:

The majority of patients on whom an esophagectomy has been performed (excluding the cervical segment cases) are able to return home within two to three weeks after operation, depending upon the distance to be traveled and the possibilities of care at home. Then there is a period of readjustment which may present difficulties and lead to anxieties from which the surgeon should seek to protect the patient by explanation and advice.

Functional disturbances of the gastrointestinal tract: In common with patients who have been subjected to a total gastrectomy, patients who have had operations of the sort described frequently complain that they do not regain a normal appetite. This may correct itself after weeks or months have elapsed, but in many cases the return of appetite is incomplete at best. This occurrence is associated with and possibly explained in part by the fact that many patients experience a functional delay in the emptying time of the stomach. The interruption of the vagus nerves is a contributing factor because of the resulting diminution in the amplitude of the gastric peristaltic activity and because of the hypertonicity of the pyloric sphincter. The result is that the stomach remains partially filled much of the time. It is a common observation among these patients that they are able to eat a large breakfast, but that they have little appetite for their noonday meal and are able to accommodate hardly any of their supper. This functional difficulty is most pronounced in the cases with carcinoma of the cardia which require excision of large segments of the stomach leaving only a small distal portion which accommodates a limited volume of food. It has been observed, however, that pronounced examples of the inability of the stomach to empty after the performance of a partial gastrectomy and esophagectomy have become much less frequent than formerly and that the difficulty arises least often in patients who have had a high esophagectomy. A possible explanation for this is that the division of the gastrocolic and gastrohepatic ligaments is now carried all the way to the level of the pylorus in every case, thus probably interrupting many of the sympathetic nerve fibers which would otherwise be overactive because of the absence of the vagus inhibition.

In evaluating the postoperative digestive function of these patients it should be kept in mind also that except in the case of lesions high in the esophagus where the whole stomach is preserved, it is necessary to resect portions of the fundus of the stomach. In some cases this causes a very large reduction in gastric volume which further limits the capacity of the patient to take food.

The inability of patients to handle large quantities of food during the first few months of their convalescence is sometimes so great that there is a progressive loss of weight. Such patients should be advised to take nothing but the most nourishing types of food and to avoid wasting

valuable space on materials, either liquid or solid, which have a low caloric content. As time goes on, however, in the majority of cases the patient's capacity for food increases as the gastric remnant enlarges and the emptying time of the stomach approximates a normal rate. In spite of this it is unusual for the patient to regain his customary weight. More often he will gain a few pounds, or in many cases he will be able merely to hold his weight at a reduced level without further loss.

It is interesting to note that although it is frequently necessary to ligate the thoracic duct, particularly in the cases where the position of the growth requires a supra-aortic arch anastomosis, no disturbance of nutrition which can be attributed to this procedure has been observed. The nutritional status of such patients does not vary in any respect from that of those whose thoracic duct remains undisturbed.

A troublesome occurrence frequently observed is the tendency to regurgitation from the stomach if a recumbent position is assumed soon after eating. All patients who have had the operation should be advised not to lie down during the first two hours after meals.

Occasionally a patient may develop diarrhea which lasts sometimes a few days, sometimes several weeks before it subsides. This is probably caused by the disturbance of function resulting from bilateral vagus section. But this phenomenon is observed in these cases much less frequently than among patients who have had a vagotomy performed in the treatment of duodenal ulcer. Relief is obtained by means of the usual symptomatic treatment.

Recurrences of dysphagia are exceedingly unusual after esophagectomy with esophagogastric anastomosis. Cicatricial stenosis of the anastomosis has been seen once. Recurrence of carcinoma at the anastomosis occurs occasionally, but the majority of the patients who succumb to the disease die from the effects of distant metastases or local recurrences within the mediastinum and retain their ability to swallow normally as long as they live.

Incisional pain: Incisional pain lasting more than a few weeks is unusual. It is a frequent observation that after the period of immediate post-operative pain is over, there is very little discomfort. If any uncomfortable sensations are experienced, they are described as a slight pain, an aching or sore feeling, or in some cases as a numbness beneath and medial to the anterior end of the incision in the abdominal and lower thoracic distribution of the terminal branches of the corresponding intercostal nerves. In many cases a transitory sensation of numbness or anesthesia in this area gives way to a period of hyperesthesia when the slightest touch gives rise to discomfort. This in turn subsides in a few weeks and the patient remains comfortable. Long-lasting incisional pain or discomfort of any kind is extremely unusual.

Dyspnea: Although a large portion of the left thoracic cavity may be occupied by the transplanted stomach, patients on whom an esophagectomy has been performed almost never experience any sensations which might make them aware of the presence of the stomach within the thorax. Gastric peristaltic sounds are occasionally heard, but they are more often noticed by other people than by the patient himself. Furthermore, after the immediate postoperative period of readjustment has gone by, there is rarely any striking dyspnea or evidence of circulatory disturbances.

Rehabilitation: The return of strength and the ability of the patient to resume an active life depend, in addition, on the condition of the patient.

Carcinoma of the esophagus are elderly, the return to a normal degree of strength may be very gradual and often never complete. It is not unusual, on the other hand, for patients to return to their customary daily routines and often to their usual occupations. The majority of them are so happy to be able to swallow normally again after a more or less prolonged period of dysphagia and chronic starvation that they usually maintain a cheerful outlook and are eager to become useful citizens once again.*

RESULTS

In a review of experience with 450 cases of carcinoma of the esophagus published in 1954, it was shown that of 182 cases where the growth involved the mid-thoracic segment, a resection could be performed in 120 instances (66 per cent), and of 242 cases where the growth was at or near the cardia, a resection was possible in 167 instances (69 per cent) [11].

The latest operative mortality of all cases from the beginning of the series in 1939 to May, 1956, is 25 per cent for cases where an anastomosis was required above the aortic arch (mid-esophagus) and 11 per cent in those involving the lower esophagus.

An analysis of the five-year survival of those who survived the operation as of May, 1956, reveals that when all cases, both favorable and unfavorable, are grouped together, there were 15 per cent of the patients with a low esophageal cancer and 6 per cent of those with a mid-thoracic growth alive after five years. On the other hand, when the cases are grouped so as to correlate the result with

* Richard H. Sweet, The Treatment of Carcinoma of the Esophagus and Cardiac End of the Stomach by Surgical Extirpation, *Surgery* 23, 952, 1948. By permission of Surgery.

the presence or absence of lymph node metastases, there were actually 32 per cent of the patients with a low growth and 23 per cent of those with a mid-thoracic growth alive after five years among those who had no positive nodes and thus had a favorable prognosis.

Finally, it should be said that of those who died of persistent or metastatic cancer, the majority were able to swallow during the remainder of their lives because of the rela-

tive rarity of recurrence of carcinoma at the anastomotic site.

Thus, it may be seen that the twofold objective that must be kept in mind in dealing with cancer of the esophagus may be realized by the employment of the operative technic herein described in a sufficient number of instances to make the effort distinctly worthwhile to the patient and gratifying to the surgeon.

Cancer of the Upper Thoracic Esophagus

Surgical Management by a Combined Right Thoracoabdominal Approach

William L. Watson

and

Raymond K. J. Luomanen

Workable surgical techniques have been devised for the management of cancer of the cervical portion of the esophagus [8] (Vol. III, Chap. 15) and for those cancers located in the middle and lower thirds [2] (Chap. 35). When, however, cancer is located in the upper segment of the thoracic esophagus, where it comes into intimate contact with the hilus of the lung and the trachea, a trying set of technical difficulties is encountered in surgical resection and anastomosis. It is believed that the one-stage, combined, right thoracoabdominal approach carried out by one or two operating teams has definite advantages.

SURGICAL TECHNIC

After the patient has been anesthetized and intubated, he is placed on the operating table in the left lateral recumbent position, inclining backward at a 45-degree angle.

INCISION

An incision is made beginning in the interscapular region, one half the distance between the vertebral border of the scapula and the posterior vertebral spines, skirting the angle of the scapula by two fingerbreadths, and extending anteriorly along the sixth rib to the costal margin.

The incision is carried down to the muscles, bleeding vessels being clamped and ligated with 0000 silk. Skivo towels are applied and the auscultatory triangle is entered by means of sharp dissection. The muscles are

elevated by blunt digital dissection so that bleeding from vessels within the muscle can be controlled by pressure from below as the muscle is divided. The sacrospinalis muscle is elevated from the proximal portion of the fifth and sixth ribs and the periosteum of the sixth rib is incised and elevated, and the sixth rib removed from the costal cartilage to within an inch of the transverse vertebral process (Figure 36-1). A 1-inch to 2-inch segment of the fifth rib proximal to the angle is similarly removed. The pleura is incised and the right thoracic cavity explored.

MOBILIZATION OF ESOPHAGUS

The collapsed right lung is retracted anteriorly and medially, exposing the middle and upper thirds of the esophagus without obstruction except for the crossing of the azygos vein (Figure 36-2). This vein is isolated as it enters the superior vena cava and divided between ligatures and transfixion sutures. The superior mediastinal pleura is incised to the apex of the chest, care being taken to avoid the vagus nerve, which at this level lies on the lateral wall of the trachea. The esophagus can then be easily isolated as it lies on the vertebral bodies just posterior to the trachea, and a Penrose drain passed around it for traction and easy identification. The lower esophagus is identified by entering the mediastinum through the inferior pulmonary ligament (Figure 36-3), and a Penrose drain is similarly passed around this uninvolved portion,

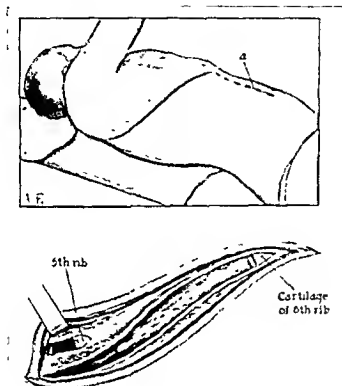


Fig. 36-1. The position of the patient on the operating table is most important. Sketch showing the 45-degree angle, the position of the right arm, and the incision along the course of the sixth rib. a: The right paramedian abdominal incision.

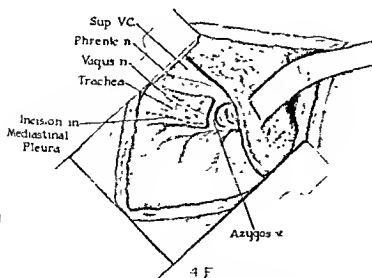


Fig. 36-2. The dotted line indicates the incision over the esophagus in the superior mediastinal pleura. The azygos vein is shown and is to be transected in the next step.

which is then freed from the prevertebral fascia, usually without difficulty. The esophageal vessels are ligated as visualized. The anterior aspect of the tumor, which usually is in intimate contact with the hilus of the lung, posterior wall of the trachea, and arch of the aorta, presents considerably more difficulty in dissection (Figures 36-4 and 36-5).

36-6B). Division of the left triangular ligament assists retraction of the liver to the right sufficiently to expose the entire cardia. Occasionally the peritoneal reflection from the stomach to the diaphragm can be more easily divided by approaching the hiatus from the chest. The hiatus is stretched and the stomach is then delivered into the right thorax through

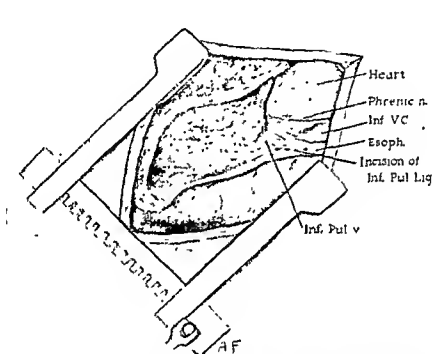


Fig. 36-3. Initial exposure on opening the right hemithorax through the bed of the resected sixth rib. The incision in the inferior pulmonary ligament is shown, revealing the intimate relationship of the esophagus and inferior vena cava.

ABDOMINAL APPROACH

If removal of the tumor seems feasible, or if the surgeon elects to do a palliative bypass operation, a second team extends the incision in right paramedian fashion to the umbilicus for exposure of the stomach (Figure 36-6A). Exploration of the peritoneal cavity for metastases is carried out. Special study of nodes about the left gastric artery and splenic vessels is essential in determining the feasibility of mobilizing the entire stomach. The stomach is freed by incising the gastrocolic omentum, preserving the vascular arch formed by the anastomosis of the right and left gastroepiploic arteries. The lesser omentum is divided, sacrificing the left gastric artery as close to its origin from the celiac axis as possible (Figure

the enlarged esophageal hiatus (Figure 36-7). Mobilization is so complete that the anastomosis can easily be carried out in the extreme apex of the thorax, or even in the lower neck. The pylorus can be delivered through the enlarged esophageal hiatus if necessary. Care must be taken not to twist or rotate the mobilized stomach on its long axis, nor to bring more stomach into the chest than is actually needed. When necessary, the right duodenal margin of peritoneum can be incised to provide further mobilization.

TRANSECTION OF ESOPHAGUS

The cardiac end of the esophagus is divided between clamps (Figure 36-8). This division can be made to include as much of the cardia

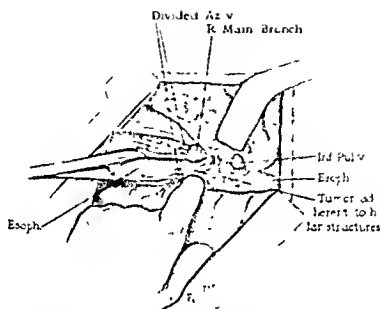


Fig. 36-4. The azygos vein has been transected and the upper third of the esophagus mobilized, revealing the cancer to be adherent to the right main-stem bronchus and hilar structures.

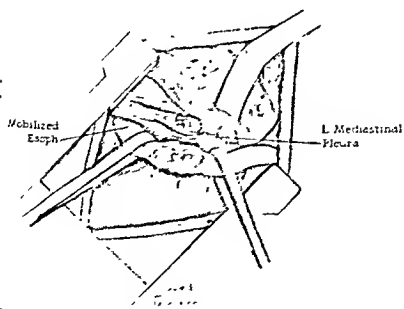


Fig. 36-5. The cancer has been dissected from the hilum and the entire thoracic esophagus mobilized.

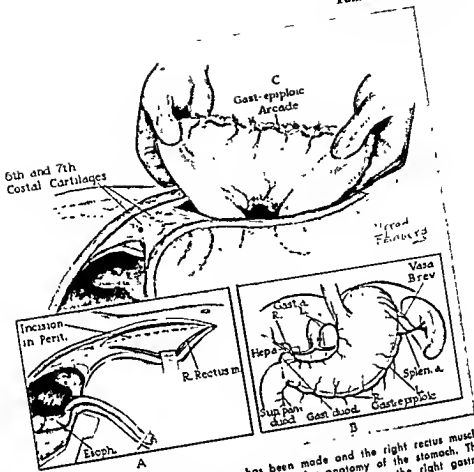


Fig. 36-6. A. The abdominal incision has been made and the right rectus muscle retracted laterally. B. Showing the essential vascular anatomy of the stomach. The left gastric artery and the vasa brevia are transected, retaining the right gastro-epiploic arcade. C. The mobilized stomach with its essential blood supply.

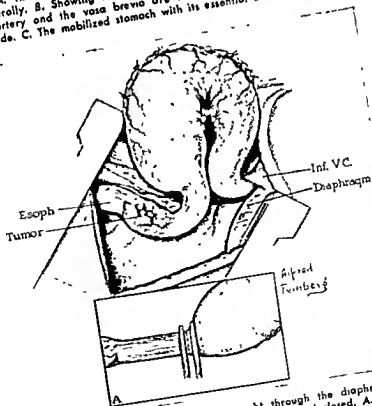


Fig. 36-7. The stomach has been brought through the diaphragmatic hiatus into the right thorax and the abdominal wound closed. A. Site of transection of cardiac end of stomach.

Cancer of the Upper Thoracic Esophagus

as need be sacrificed if the blood supply appears compromised. The divided stomach is inverted with a continuous Parker-Kerr suture of 00 chromic catgut on an atraumatic needle. This row is then further invaginated with a row of interrupted mattress sutures of 000 silk.

GASTROESOPHAGEAL ANASTOMOSIS

The stomach is sutured to the posterior wall of the esophagus well proximal to the neo-

bert sutures of 000 silk tied within the lumen. The mucosa of the esophagus and the mucosa of the stomach are approximated with similar sutures posteriorly. These three rows of sutures are then continued around anteriorly to complete the anastomosis.

CLOSURE

The stomach is then attached to the mediastinal pleura so as to relieve the suture line of any possible tension (Figure 36-10). The

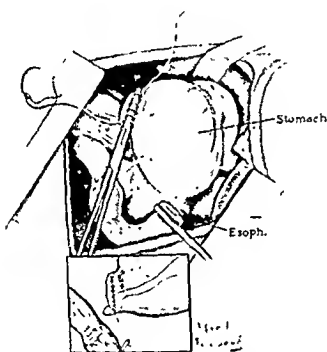


Fig. 36-8. Closure of the gastric cardia.

plasm with interrupted mattress sutures of 000 silk (Figure 36-9). At this point, care must be exercised to maintain the proper relationship of the lesser curvature of the stomach by avoiding its tendency to rotate or twist upon itself. After the posterior row of sutures has been laid, approximating the esophagus to the stomach, the esophagus is divided several centimeters proximal to palpable tumor. A frozen section from this level will confirm the adequacy of the excision. A button, approximately 2 cm. in diameter, is excised from the anterior wall of the stomach just inferior to the open end of the esophagus. The muscularis of the esophagus is then approximated to the serosa and muscularis of the stomach with a row of interrupted Lem-

mediastinal pleura is closed over the anastomosis site with interrupted sutures. The stomach is further attached to the paravertebral gutter. A No. 30 rectal catheter with extra holes is inserted into the right thorax through a stab wound in the tenth intercostal space, sutured to skin, and connected to an underwater trap. A solution of 50 cc. of saline containing 1 Gm. of streptomycin and 500,000 units of penicillin is placed in the chest cavity.

The involved intercostal nerves are isolated and injected with a solution of procaine in oil and the wound is closed in layers. The parietal pleura and intercostal muscles are approximated with interrupted sutures of 00 silk that are tied as the adjacent ribs are

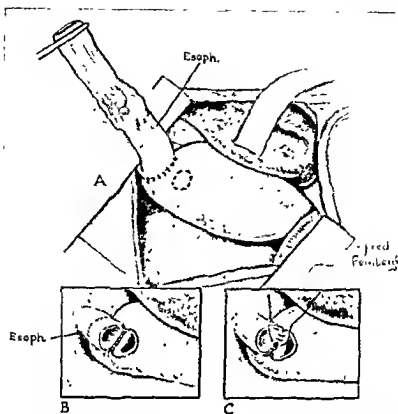


Fig. 36-9. A. First step in the three-layer anastomosis of the proximal esophagus to the gastric cardia. Dotted line indicates the button of gastric wall to be excised. B. Second suture line—muscularis of esophagus to muscularis of serosa of stomach. C. Third suture line—mucosa to mucosa.

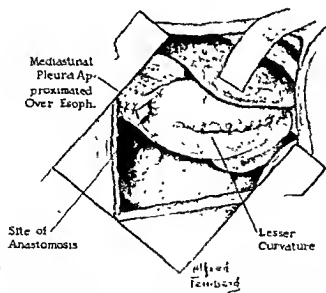


Fig. 36-10. The anastomosis is complete and the mediastinal pleura approximated over the esophagus. The lesser curvature of the stomach is in the right lateral position; this prevents rotation of the stomach at the pylorus.



Fig 36-11. (Left) Preoperative esophagogram showing cancer of the upper esophagus. (Right) Esophagogram showing the anastomosis in the lower right neck by Murphy button.

held in approximation. The chest muscles are approximated with 000 silk, and the posterior rectus sheath and the peritoneum in the abdominal wound are closed with a

continuous suture of No. 1 chromic catgut, the anterior rectus sheath is approximated with interrupted sutures of 000 silk or No. 32 steel wire. The subcutaneous tissues, fascia, and skin of the entire length of the incision are closed with 0000 silk. A dry dressing is applied with broad strips of elastoplast. If two operating teams are employed, the abdominal incision is closed while the intrathoracic anastomosis is being carried out.

RESULTS

The first esophagectomy at Memorial Hospital was a Torek type procedure done in 1940, and since then there have been 217 successful surgical excisions of the esophagus for cancer. Of these, twenty-five were cervical esophagectomies and seven patients had combined cervicothoracic esophagectomy. Of the one hundred ninety-two patients who had a resection by means of a thoracic approach, fifty-seven (29.6 per cent) had a resection of the right-sided, one-stage, combined thoracoabdominal type. In ten patients the anastomosis between stomach and cervical esophagus was made through a right lower cervical



Fig 36-12. Clinical photograph of patient after the operation, showing the combined right thoracoabdominal incision and the healed cervical incision.

incision. Two other patients had an anastomosis between stomach and pharynx.

In this series of fifty-seven resected cases, there were fifteen (26.3 per cent) postoperative deaths.

ADVANTAGES AND DISADVANTAGES OF THE COMBINED RIGHT THORACO- ABDOMINAL APPROACH

ADVANTAGES

The combined right thoracoabdominal approach for cancer of the upper thoracic

4. The exposure obtained by this procedure readily permits gastroesophageal anastomosis at, and occasionally above, the superior thoracic aperture.

5. At the completion of the operation, the stomach lies in the mediastinum in a more satisfactory anatomic position. There is practically no tension, and the blood supply is excellent (Figure 36-13).

6. If a resection cannot be accomplished because of the extent of the cancer, one is still permitted to do a palliative by-pass operation (Figure 36-14), which provides more tempo-

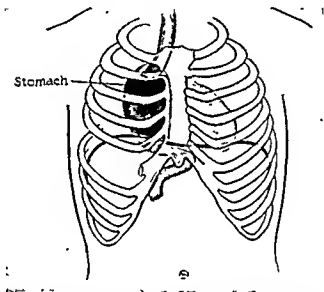


Fig. 36-13 Diagram indicating the approximate site of gastroesophageal anastomosis and the altered mediastinal relationship.

esophagus has been shown to have the following advantages:

1. It permits better cancer surgery because a more extensive resection of potentially involved esophagus can be done with a minimum of technical difficulty.

2. It affords an increased range of resectability in cases in which cancer is closely adherent to bronchus and the arch of the aorta, because the dissection in this region can be carried out under direct vision.

3. There is less danger of accidentally entering the opposite pleural cavity, and, when a segment of opposite pleura must be resected because of extension of cancer, it can be done under direct vision.

rary relief than does a Janeway gastrostomy [7].

DISADVANTAGES

The disadvantages of the procedure are as follows:

1. There are added anatomic dangers at the diaphragmatic level because of the proximity of the inferior vena cava, pleura of the left chest cavity, and hepatic vein, which may be injured when working through the esophageal hiatus (Figure 36-15).

2. The degree of abdominal exposure may be lessened by the adverse position of an enlarged liver.

3. Simultaneous surgery in the thorax and

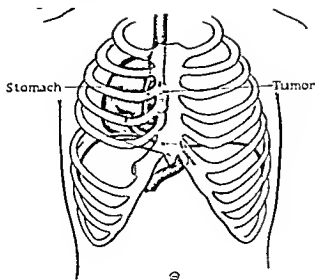


Fig. 36-14. Even though a palliative resection cannot be done, it is sometimes possible to bring the stomach up into the chest and anastomose it proximal to the esophageal cancer. This bypass procedure seems to afford more palliation than a simple gastrostomy.

abdomen increases the likelihood of shock.

4. Two operative wounds add to the theoretic danger of wound sepsis.

5. The upper abdominal wound does add

to the patient's postoperative discomfort, and may interfere with adequate pulmonary ventilation.

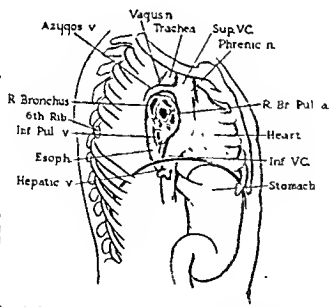


Fig. 36-15. Diagrammatic sketch showing the important anatomic structures encountered in the right thoracoabdominal approach to esophagectomy. Note the relationship of the esophagus to the inferior vena cava and hepatic vein.

incision. Two other patients had an anastomosis between stomach and pharynx.

In this series of fifty-seven resected cases, there were fifteen (26.3 per cent) postoperative deaths.

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6. If a resection cannot be accomplished because of the extent of the cancer, one is still permitted to do a palliative by-pass operation (Figure 36-14), which provides more tempo-

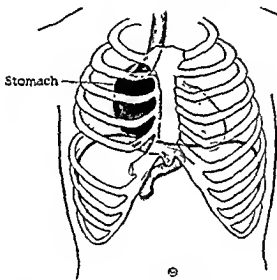


Fig. 36-13. Diagram indicating the approximate site of gastroesophageal anastomosis and the altered mediastinal relationship.

esophagus has been shown to have the following advantages:

1. It permits better cancer surgery because a more extensive resection of potentially involved esophagus can be done with a minimum of technical difficulty.

2. It affords an increased range of resectability in cases in which cancer is closely adherent to bronchus and the arch of the aorta, because the dissection in this region can be carried out under direct vision.

3. There is less danger of accidentally entering the opposite pleural cavity, and, when a segment of opposite pleura must be resected because of extension of cancer, it can be done under direct vision.

rary relief than does a Janeway gastrostomy [7].

DISADVANTAGES

The disadvantages of the procedure are as follows:

1. There are added anatomic dangers at the diaphragmatic level because of the proximity of the inferior vena cava, pleura of the left chest cavity, and hepatic vein, which may be injured when working through the esophageal hiatus (Figure 36-15).

2. The degree of abdominal exposure may be lessened by the adverse position of an enlarged liver.

3. Simultaneous surgery in the thorax and

BY-PASSING PROCEDURES

Esophagoplasty is sometimes indicated as a palliative by-pass procedure if it is impossible to remove the primary tumor (Figure 37-3).

FOR COMPLICATIONS OF OTHER TREATMENT

If a complication such as tracheoesophageal fistula, perforation into the mediastinum,

the stomach or the small bowel is mentioned for historic interest. Multiple operations are required with numerous long hospitalizations. Strictures at either end of the tube are common, especially at the stomach end where the gastric secretions often ulcerate the skin tube. Food tends to obstruct at the level of the clavicle and also at the level of the abdominal fascia. The subcutaneous tube tends to be



Fig. 37-1. The completed Tarek operation. In this patient, the operation was done prior to the adoption of the intrathoracic or intracervical types of anastomosis. The rubber feeding tube conjoins the prethoracic esophagostomy with a Janeway gastrostomy made with the remnant of stomach. This is an unsatisfactory mechanical arrangement and is difficult to control. This patient later had a prethoracic esophagus constructed, using the skin of the chest wall. (From G. T. Pack and W. L. Wahan [23], courtesy *Archives of Surgery*)

or stricture develops following radiation therapy, an early by-passing procedure may be performed.

METHODS OF ESOPHAGOPLASTY

The various methods described for reconstruction of the thoracic esophagus are presented in Table 37-1.

USE OF SKIN TUBES

The use of a tube of skin created to bridge a defect between the cervical esophagus and

unsightly, particularly in women, although this can be overcome by later transplanting the tube within the chest.

Occasionally, however, it may be necessary to use a small supplemental skin tube in the region of the neck to bridge a short gap between an organ transplant and pharynx or cervical esophagus.*

* EDITORIAL NOTE. The editors have successfully used a split-thickness skin graft to reconstruct the esophagus. The graft takes well. One patient so treated is well five years after resection of an extensive esophageal cancer, with a functioning skin graft which replaced her resected cervical

Methods of Reconstruction of the Thoracic Esophagus

Theodore R. Miller
and

Charles D. Sherman, Jr.

On May 21, 1894, Bircher performed the first stage of a subcutaneous esophagoplasty using a tube made of the patient's skin. Esophageal reconstructions were first done to by-pass or repair strictures caused by the ingestion of caustic materials. During the past twenty years, indications have broadened to include patients with atresia of the esophagus or tracheoesophageal fistula, patients who have had resection of the esophagus for esophageal varices, stricture secondary to esophagitis, or cancer, and in some instances for complications of x-ray treatment of esophageal cancer.

Volcker is credited with the first attempt at resection of the esophagus, but it was Torek [44] who in June, 1913, accomplished the first successful resection of the thoracic portion of the esophagus for carcinoma. According to his description of the operation, a trans-thoracic approach was used. After the esophagus was ligated in continuity and divided and the distal stump turned in by purse-string sutures, the thoracic esophagus was dissected free of its bed by blunt and sharp dissection. An incision was then made in the neck along the anterior border of the left sternomastoid muscle. Dissection was completed from above and below and the esophagus was drawn out into the neck. The patient was left with an esophagostomy and a gastrostomy had to be constructed for feeding purposes.

In spite of Torek's comment, when he reported his case after seven years' survival, that the "condition of the patient allowed a

comfortable and happy existence," there is no question that most patients are not happy living with a permanent esophageal fistula and a gastrostomy. Because of the great difficulty in re-establishing gastrointestinal continuity following subtotal resections of the Torek type, most surgeons have compromised in the length of the esophagus resected and have elected to use the stomach for primary esophagogastrostomy. The authors believe that the proper procedure for treating esophageal cancers, except those in the lowermost portion, consists of a total thoracic esophagectomy together with removal of a small segment of the upper part of the stomach and the left gastric artery with the surrounding nodes (Figure 37-2).

INDICATIONS FOR ESOPHAGOPLASTY IN PATIENTS WITH CARCINOMA

FOLLOWING RESECTION FOR TUMOR

A resectable cancer of the middle or upper portion of the thoracic esophagus is the prime indication for esophagoplasty. Although there is a separate chapter dealing with cancer of the cervical esophagus (Vol. III, Chap. 15), it should be mentioned that cancers of this location sometimes extend downward so far that adequate excision means resection of the esophagus down into the midthoracic region. The problem of esophagoplasty to bridge such a long gap then is approximately the same as that following subtotal esophagectomy of the Torek type.

TABLE 37-1.—METHODS OF RECONSTRUCTION OF THE THORACIC ESOPHAGUS

- I. Dermatoesophagoplasty; use of skin alone:
 - A. Full thickness skin (Bircher)
 - B. Thiersch inlay grafts lining skin tunnel (Esser)
- II. Gastroesophagoplasty:
 - A. Salpingogastroesophagoplasty; formation of tube from stomach
 1. From greater curvature (Beck-Jianu-Halpern-Gavrilu)
 2. From anterior surface (Hirsch)
 - B. Gastroesophagoplasty; use of entire stomach:
 1. Antiperistaltically (Fink)
 2. Isoperistaltically (Kirschner)
- III. Jejunoesophagoplasty; use of small bowel alone:
 - A. Mobilization of jejunal segment anterior to transverse colon (Roux)
 - B. Mobilization of jejunal segment through lesser sac (Herzen)
- IV. Jejuno-dermatoesophagoplasty; use of small bowel and skin tube:
 - A. Y-anastomosis of jejunum (Wullstein)
 - B. Jejunal segment anastomosed to stomach (Lecser)
- V. Colocoesophagoplasty:
 - A. Transverse colon
 1. Isoperistaltic (Kelling)
 2. Antiperistaltic (Vulliet)
 - B. Ascending colon (Roith)

SOURCE: A. Ochener and N. Owens [20].

atony of the stomach secondary to cutting the vagus nerves, with encroachment on the lung and other intrathoracic structures; esophagitis, and stricture formation. Regurgitation of gastric juice into the pharynx and occasional aspiration often occur. In a certain percentage of cases the stomach cannot be made to reach the neck. Reports on the use of this procedure usually note a rather high mortality rate.

USE OF SMALL BOWEL

Although there are difficulties in using small bowel, circumstances exist when its use in reconstruction is indicated. The jejunum can be used after the method of Yudin [49], Robertson [28], and others; or the ileum can be used with the pedicle based upon the ileocolic artery (Sberman).

Introthoracic Jejunoesophagoplasty

The use of jejunum, originally proposed by Wullstein [48], Roux [29], and Herzen [11], is beset with difficulties. The first difficulty lies in the fact that in 30 to 60 per cent of cases the loops cannot be raised with sufficient length to reach the neck without necrosis, owing to poor blood supply. This makes placement within the chest hazardous. Attempts have been made to increase the blood supply to the transplanted jejunum by raising it in stages, as one would increase the blood supply to a skin tube by raising it in stages. This occasionally has proved satisfactory, but there have been a number of instances where secondary exploration has revealed so much scarring of the transplant, particularly around the blood vessels, that it is more difficult to raise a transplant at a second stage than it was originally. Russian and French surgeons have increased the blood supply by dividing the fascial attachments at the root of the mesentery, freeing the superior mesenteric artery so that it would turn upward more easily. A third method of avoiding necrosis involves taking the jejunal transplant as high in the chest as it will go without tension as a first stage and later remobilizing the loop and bringing it the rest of the way to the neck. After the jejunum has been brought high in the chest or to the thoracic inlet as an initial stage, remobilization may include dividing of smaller arcades which may not be divided at the original procedure, allowing greater length to be obtained. Other procedures, such as anastomosing the jejunal blood supply to the internal mammary artery or multistaging the procedure so that the jejunal transplant can be completely divided from its blood supply and encased in a tube of skin, are historic procedures and not of any practical significance today.

Another problem relates to the anastomosis of the lower end of the transplant. If the stomach is by-passed, the patient's nutrition is impaired and the isolated gastroduodenal segment may ulcerate or hemorrhage. If the jejunum is anastomosed into the stomach, peptic ulceration of its lower end becomes a possibility. Yudin, who had had a tremendous experience with esophageal resection, always

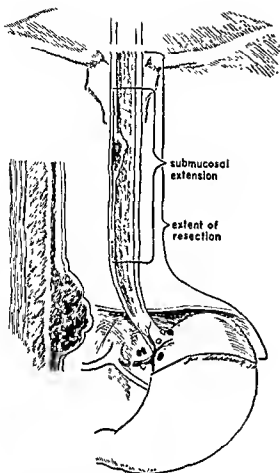


Fig. 37-2. The drawing shows the long submucosal extension of tumor and skip metastases, which can involve lengths of from 15 to 20 cm. or more. It also shows the recommended incision necessary to encompass this extension and the left gastric nodes that are often involved in cancers of the middle and upper thirds of the esophagus.

USE OF STOMACH

The use of an antiperistaltic tube from the greater curvature of the stomach was first proposed in 1905 by Beck and Carroll [3] and successfully employed by Jianu, a Rumanian surgeon, in 1912 [11a]. Mes [16] in 1948 made an isoperistaltic tube from the entire greater curvature which, when placed as a subcutaneous transplant, would reach the level of the pharynx without necrosis. Wangenstein [46] has reported two successful tubes of this type. Gavrilu is said by Heimlich [9] to have reconstructed the esoph-

agus and two thirds of her thoracic esophagus (see Vol. III, p. 233). The graft was supported by a plastic stent consisting of a Bernan tube. When esophageal cancers cannot be resected and produce obstruction, various plastic prostheses are available to maintain patency of the esophagus; these prostheses do not interfere with radiation therapy, if this be indicated [31a].

agi of 52 patients with an antiperistaltic tube of the stomach with 100 per cent success. It has been stated that these antiperistaltic tubes ultimately change their peristalsis into an isoperistaltic direction. Heimlich has successfully replaced the esophagus with a reversed gastric tube in ten patients [10]; he states that this procedure provides a physiologic means of esophageal replacement (see Figures 37-5 through 37-8). A major disadvantage of this procedure is that the removal of a small segment of the upper part of the stomach, including the left gastric artery with the surrounding lymph nodes, is not technically feasible.

The use of the entire stomach placed subcutaneously, both in an antiperistaltic and an isoperistaltic manner, has been recorded as a method of replacing the esophagus.

The most common method of reconstructing gastrointestinal continuity following esophagectomy has been an esophagogastric anastomosis (see Chap. 35). The higher above the aortic arch one makes an anastomosis, the greater becomes the morbidity and mortality. Disadvantages in the use of a high esophagogastric anastomosis include dilatation and

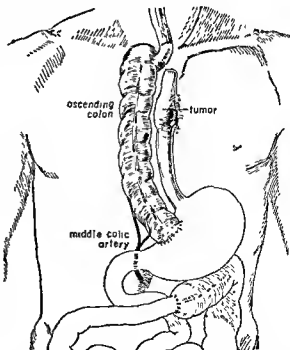


Fig. 37-3. By-passing procedure. If a tumor cannot possibly be excised, a palliative by-passing procedure through the substernal tunnel is used. The distal esophagus in the neck is closed, and an end-to-end anastomosis between the proximal cervical esophagus and the ileum (or cecum) is done.

by-passed the stomach because of the danger of peptic ulceration of the jejunal segment. Some writers have reported that 20 to 25 per cent of their patients have poor nutrition when the stomach is by-passed. There have been several instances of ulceration and hemorrhage from the isolated gastroduodenal segment when the stomach is by-passed, but these have been predominantly in children, and it may be that this is not of real significance in adults in whom a vagotomy has been done. There is recent experimental evidence (Merendino [15]) to indicate that peptic digestion of the jejunum, when it is anastomosed into stomach, is rare. Montenegro [18], on the basis of experimental evidence, suggests that it is best to anastomose the transplant to the uppermost portion of the stomach.

Subcutaneous Antethoracic Jejunoesophagoplasty

Although this procedure now is mainly of historic interest, one of us (T. R. M.) has several patients with long-term cures who have been subjected to this reconstructive operation.

The original Torek operation combined with subtotal gastrectomy and wide node dissection leaves the patient with a cervical esophageal fistula and a gastrostomy, which is then reconstructed by staged procedures as illustrated in Figure 37-4.

As has been noted by others, the jejunum rapidly parasitizes itself on the surrounding structures, so that there need be little concern over the circulation of the jejunal limb.

USE OF COLON

Subcutaneous colon transplants were originally described by Kelling [12] and by Vulliet [45] in 1911 and had been used primarily to by-pass inoperable carcinomas. Following World War II, this method of reconstruction was revived in Western Europe and in 1951 the French were the first to report its use intrathoracically. Currently the right ileocolon, the transverse colon, and the descending colon are all being used both antiperistaltically and isoperistaltically. One of us (C. D. S.) has utilized the ileocolon placed in a sub-sternal position. The advantages of this pro-

cedure are (1) the ease with which an adequate length of transplant can be prepared with unquestioned viability, and (2) the seeming resistance of colon to peptic digestion, thereby allowing the lower end of the transplant to be anastomosed into the stomach without fear of ulceration. There have been about two hundred of the ileocolic transplants performed in the United States (Sherman). The mortality has been low (5 per cent to 10 per cent). The functional results are good.

TECHNICS OF ESOPHAGOPLASTY

GENERAL CONSIDERATIONS

If there is a possibility that a colon transplant may be used, the colon should be prepared by a low-residue diet progressing to a clear liquid diet for the last two days, Sulfathalidine and/or neomycin to sterilize the bowel, and enemas and cathartics. A barium enema helps to rule out abnormalities of the colon.

In order to allow two operating teams to work simultaneously in the chest and abdomen, the patient is placed at a 30-degree to 40-degree angle and the procedure is started by the thoracic team, which resects the fifth rib through a right anterolateral exposure. If the cancer proves resectable, the abdominal team makes a mid-line incision in the abdomen extending to the xiphoid. If the final decision is to do an esophagectomy and reconstruction in one stage, the abdominal team resects the upper part of the stomach and the lymph nodes along the left gastric artery and prepares the transplant. The thoracic team divides the esophagus at the inlet, closing the superior portion with a continuous suture to prevent drainage of saliva into the thorax after closing the chest. Frozen-section examination of the distal portion of the divided esophagus should be done, which if positive for cancer necessitates a higher resection. Because of the continuous submucosal spread of tumor and skip metastases in a seemingly normal esophagus, the authors have had to resect as high as the pharynx before obtaining a negative frozen section in some patients, even though the primary tumor was in the midthoracic esophagus. The specimen then is delivered from above downward through

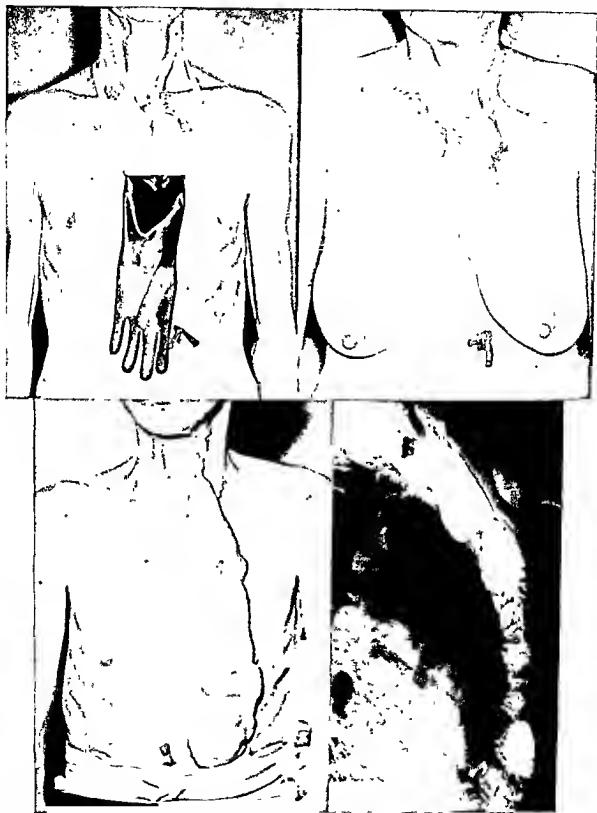


Fig. 37-4. Subcutaneous antethoracic esophagojejunal reconstruction. (Top left) Control of the salivary fistula which is formed as a part of the first stage. The fistula is encouraged to close partially, and a condom attached to a rubber bag or glove is used for the collection of saliva. Temporary stage. (Top right) Esophageal anastomosis just below the clavicle. A subcutaneous tunnel is fashioned in the chest wall, through which the proximal segment of jejunum is brought from the abdomen through the chest wall for anastomosis to the proximal esophagus. (Bottom left) Subcutaneous antethoracic jejunal substitution for esophagus. (Bottom right) Lateral esophogram of antethoracic esophagus.

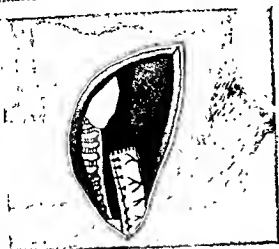


Fig 37-7. Use of reversed gastric tube to replace esophagus. Through the incision in the neck the cervical esophagus has been divided. Its distal end has been closed and has retreated into the thorax. The proximal end of the esophagus has been anastomosed and to end to the reversed gastric tube. The gastroepiploic vessels are seen accompanying the gastric tube. (From a film produced by Dr. Henry J. Heimlich, by Baxter Laboratories)

vertebral fascia to hook the cervical esophagus and bring it up into the wound. If the frozen section has shown tumor in the submucosa, then additional cervical esophagus is resected. The proximal portion is then ready to be anastomosed to the transplant of stomach, small bowel, or colon (see below)

GASTRIC ESOPHAGOPLASTY

The technic for performing an esophago-gastric anastomosis is described in Chapter 35.

The technic for employing a gastric tube to replace or by-pass the esophagus, as described by Heimlich [9], is illustrated in Figures 37-5 through 37-8.

JEJUNAL ESOPHAGOPLASTY

Care is exercised to pick the largest jejunal vessel that will give a sufficient length of transplant by dividing the branches proximal to it. Usually the fourth, fifth, sixth, or occasionally the seventh branch will prove to be the largest vessel. The peritoneum on both sides of the mesentery is elevated by the injection of 0.5 per cent Novocain subperitoneally, and it is then excised from the root of the mesentery toward the bowel (Figure 37-9). The arteries and veins are then ligated separately near the root of the mesentery, dividing suc-

cessively the next proximal one beginning with the artery selected to supply blood to the transplant. In this manner a length of viable jejunum sufficiently long to reach the neck can often be raised. Occasionally, to increase length, secondary areades in the midportion of the mesentery may be divided if the collateral circulation of the marginal artery near

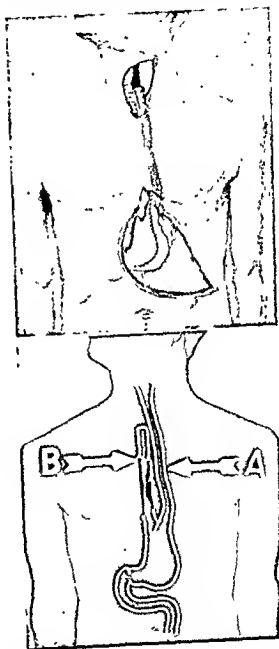


Fig 37-8. Use of reversed gastric tube to replace esophagus. (Top) The completed operation. (Bottom) The functions of the esophagus can now be performed by the reversed gastric tube (arrow A). The diseased esophagus (arrow B) is nonfunctioning. It can be resected if an operable carcinoma is present; otherwise, it is left in situ. (From a film produced by Dr. Henry J. Heimlich, by Baxter Laboratories)

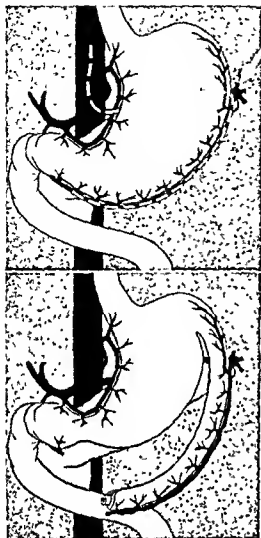


Fig 37-5 Use of reversed gastric tube to replace or bypass esophagus. (Top) The spleen has been resected. (Arrow) Ligated splenic vessels. The dash line indicates the blood flow directed from the splenic vessels into the left gastroepiploic vessels to supply the greater curvature of the stomach. (Bottom) An incision has been made into the antrum and extended parallel to the greater curvature. The gastric tube thereby formed remains attached to the stomach at the fundus (From a film produced by Dr. Henry J. Heimlich; by Baxter Laboratories)

the hiatus into the abdomen to the abdominal team.

Unless the patient is in excellent condition, reconstruction should be delayed. After closing the chest, the proximal esophagus is brought out to the neck and a gastrostomy is done. If the reconstruction is to take place immediately, the thoracic team closes the chest and then makes a four-inch incision along the anterior border of the left sternocleidomastoid. The esophagus is approached between the strap muscles and the carotid

sheath, taking care to avoid injury to the recurrent nerve. One's finger easily enters the plane between the esophagus and the pre-

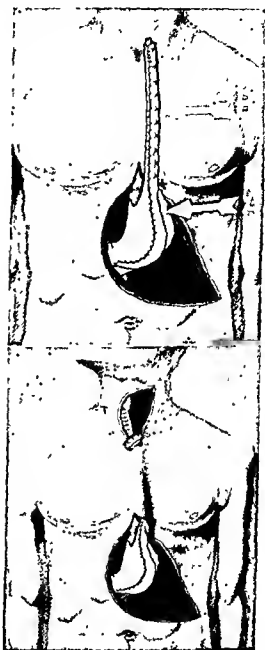


Fig 37-6 Use of reversed gastric tube to replace esophagus. (Top) The gastric tube has been reversed and lies on the chest. The anterior and posterior walls of the stomach have been approximated, completing the gastric tube and reconstituting the stomach. A rubber catheter is seen emerging from the gastric tube; this has been used as a mold on which the tube is reconstructed and is removed at this time. The tail of the pancreas (arrow A) has been freed and carries the splenic vessels to the costal margin, permitting the gastroepiploic vessels (arrow B) to accompany the gastric tube to the neck. (Bottom) The reversed gastric tube has been drawn through a subcutaneous tunnel to the neck. (From a film produced by Dr. Henry J. Heimlich, by Baxter Laboratories.)

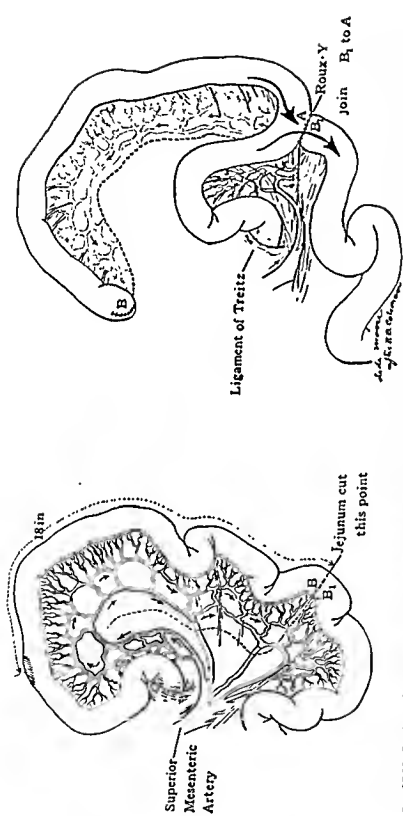


Fig. 37-10. Esophagoplasty; Roux "Y" construction after method of Reinheff. Preservation of first jejunal branch of the superior mesenteric artery. The large arrows indicate the direction of passage of food, bile, and pancreatic juice. (from J. I. Reynolds and J. P. Young, Jr. [27], *Courtesy Surgery*.)

the bowel is adequate. Care must be taken throughout the procedure not to rupture or damage the small vessels, which might necessitate ligation of essential collaterals. One must also be careful about tension on the veins that may cause thrombosis or rupture of these friable vessels. If the transplant appears viable, it may be passed posterior to the stomach and through the mediastinal tunnel to the neck and anastomosis accomplished as described below for right ileocolic esophago-

ILEAL ESOPHAGOPLASTY

The ileocolic artery is longer and larger than any of the jejunal branches and can be used as the arterial supply to an isoperistaltic loop of ileum (Sherman) (Figure 37-11). A small segment of cecum or ascending colon can be left attached to the transplant and this segment then anastomosed into the anterior wall of the stomach. This allows the possibility of the mucus from the cecum affording some added protection against peptic

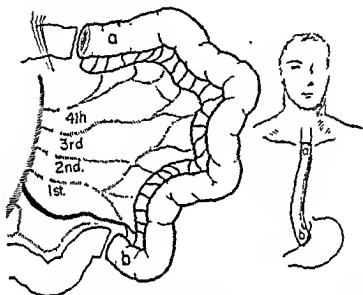


Fig. 37-9. Esophagectomy having a jejunal transplant. First, the largest branch (4th, 5th, 6th, or 7th) at the upper jejunal artery is selected as the blood supply and then the arterial branches are divided proximally in succession. Arteries and veins are ligated separately until enough length is obtained. The jejunum is then divided at appropriate points near a and b and the transplant is passed through the substernal tunnel to the neck. The end a is anastomosed to the cervical esophagus and the end b to the stomach. The blood supply lies posterior to the stomach.

goplasty. While the distal end may be planted to the gastric remnant, it is perhaps better to leave the stomach isolated, obviating the risk of peptic ulceration at the lower end of the jejunal segment. Heineke-Mikulicz pyloroplasty and gastrostomy are supplemental measures that are carried out prior to closing the abdomen. If, during the preparation of the transplant, it becomes obvious that not enough length can be raised, the attempt must be abandoned. If a segment of howel, already raised, becomes nonviable, it must be resected and some other type of reconstruction performed.

digestion of the lower end of the transplant. The proximal ileum is then taken to the neck through the substernal tunnel for anastomosis with the cervical esophagus or pharynx.

RIGHT ILEOCOLIC ESOPHAGOPLASTY

For the reconstruction of the entire thoracic esophagus, the right ileocolic transplant has proved most satisfactory. Although the number and size of the arteries to the right half of the colon and terminal ileum vary considerably, the blood supply through the middle colic arteries is almost always sufficient to give adequate nourishment to the

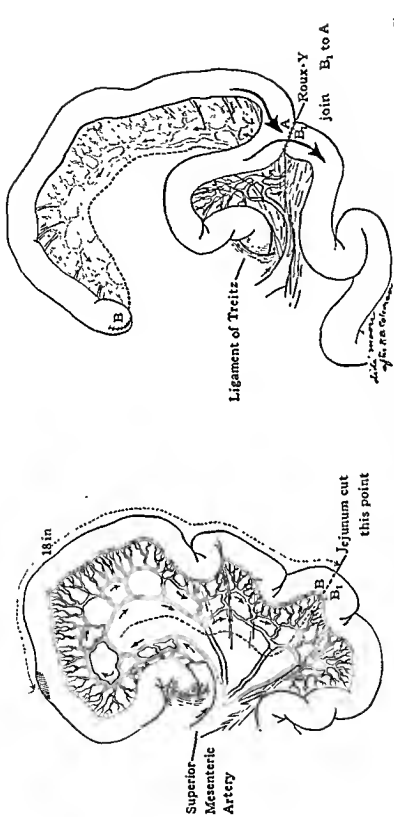


Fig. 37-10. Esophagoplasty; Roux "Y" construction after method of Reinhardt. Preservation of first jejunal branch of the superior mesenteric artery. The large arrows indicate the direction of passage of food, bile, and pancreatic juice. (From J. T. Reynolds and J. P. Young, Jr. [27], *Cautery Surgery*.)

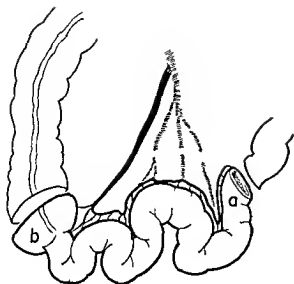


Fig. 37-11. The isoperistaltic ileal transplant. The ileocolic artery is the largest and longest of all arteries supplying the small intestine. Although this has been the least used of all transplants, it may prove to be one of the best. The mucus production by the cecum helps protect it against peptic digestion when it is anastomosed into the stomach. The size and toughness of the ileum make it a good structure to anastomose to cervical esophagus.

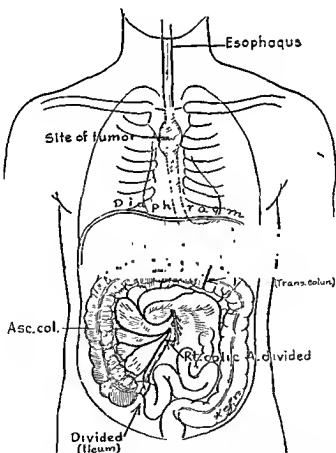


Fig. 37-12. Esophagoplasty using right ileocolic transplant. After mobilizing the right colon and testing for the adequacy of the collateral circulation through the middle colic artery, the ileocolic vessels are divided. The ileum is divided four to six inches from the ileocecal valve and the transverse colon is divided near its midportion. (From E. B. Mahoney and C. D. Sherman, Jr. [14], courtesy Surgery.)

entire transplant. The exposure is through a long mid-line or right paramedian incision extending from the xiphoid to below the umbilicus. Mobilization of the right colon is performed by cutting the lateral attachments of the ascending colon and cecum and dissecting in the avascular retroperitoneal region. The hepatic flexure is similarly dissected. This permits the right half of colon and terminal ileum to be lifted out of the abdomen so that an estimate can be made of the character of its blood supply and of the length of the

colon to the terminal ileum. The ileocolic artery and veins are ligated separately close to their origin in the root of the mesentery so as not to damage collateral vessels closer to the cecum. The transplant can now be swung up over the chest wall to the neck to evaluate its length. Care is taken again not to damage the collateral circulation and particularly the veins, which are more friable than the arteries and are just as important to the support of the transplant.

The substernal tunnel is very easily created

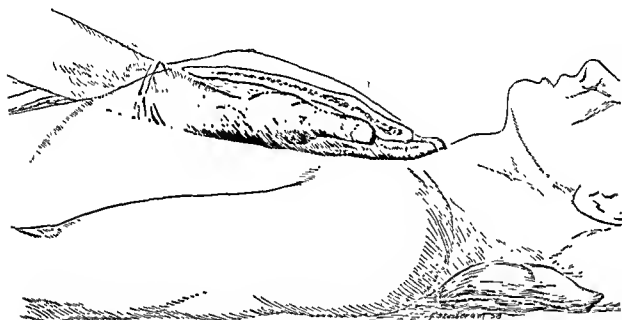


Fig. 37-13. Esophagegastropasty using right ileocolic transplant. After separating the diaphragm from the xiphoid, dissection of the substernal tunnel is easily and quickly accomplished by blunt finger and hand dissection upward until the fingers enter the neck wound.

transplant which can be raised (Figure 37-12). Unless there is some obvious anomaly of the colon or its blood supply, testing of the collateral blood supply to the transplant through the middle colic artery is done by placing arterial clamps upon the ileocolic artery and those few collaterals coming from the ileal vessels so that the only blood supply comes through the middle colic artery. Routine appendectomy is performed while one waits to evaluate the efficiency of the collateral circulation. Almost always, this collateral circulation will prove sufficient and, accordingly, the ileum is divided about six or seven inches from the ileocecal valve, care being taken not to damage the collateral circulation through the marginal artery of the

by continuous upward dissection of the fingers and hand until the fingers can be seen through the neck incision just above the suprasternal notch (Figure 37-13). The transplant is passed posterior to the stomach through the gastrohepatic ligament, then up through the substernal tunnel to the neck (Figure 37-14). It is preferable to push the transplant with the hand rather than to do any excess pulling from above with a suture or clamp. At the neck a wide aperture to the thoracic inlet is made by dividing the attachments of the strap muscles and part of the sternocleidomastoid muscles, and by sharp dissection to divide all the fascial tissues.

With the transplant in place and making certain that there is no tension on the blood

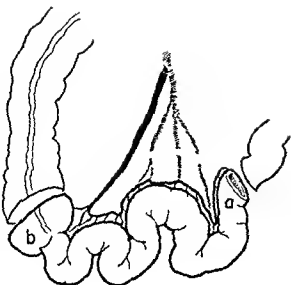


Fig. 37-11. The isoperistaltic ileal transplant. The ileocolic artery is the largest and longest of all arteries supplying the small intestine. Although this has been the least used of all transplants, it may prove to be one of the best. The mucus production by the cecum helps protect it against peptic digestion when it is anastomosed into the stomach. The size and toughness of the ileum make it a good structure to anastomose to cervical esophagus.

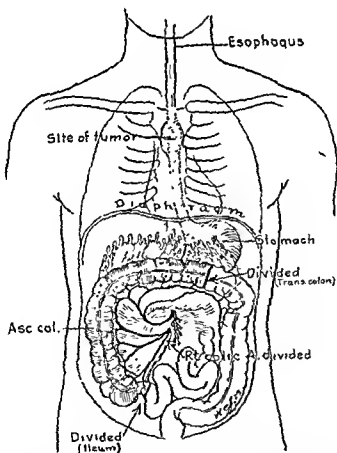


Fig. 37-12. Esophagectomy using right ileocolic transplant. After mobilizing the right colon and testing for the adequacy of the collateral circulation through the middle colic artery, the ileocolic vessels are divided. The ileum is divided four to six inches from the ileocecal valve and the transverse colon is divided near its mid portion. (From E. B. Mahoney and C. D. Sherman, Jr. [14], courtesy Surgery.)

Bilateral chest catheters are inserted. If this is omitted, each hemithorax should be aspirated before the patient leaves the operating room and an x-ray should be taken in the immediate postoperative period to prove the absence of pneumothorax.

LEFT COLON ESOPHAGOPLASTY

This transplant can be based upon a pedicle containing the middle colic artery and thus raised in an antiperistaltic manner, carrying the descending colon to the neck. On the other hand, an equally good, probably better-func-

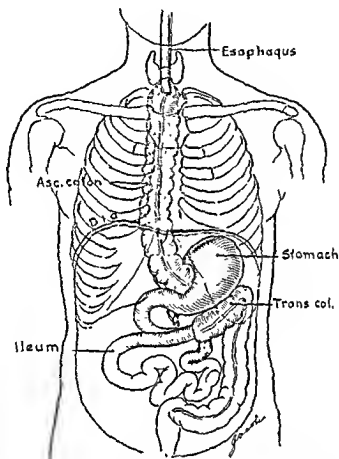


Fig. 37-15. Esophagoplasty using right ileocolic transplant. The completed operation. The cecum or ileum has been anastomosed to the cervical esophagus in the neck. The lower end of the transplant has been anastomosed into the anterior wall of the stomach, avoiding sagging of colon below the anastomosis. Bowel continuity has been re-established by careful end-to-end anastomosis of ileum to left transverse colon, using a single layer of interrupted silk. (From E. B. Mahoney and C. D. Sherman, Jr. [14], courtesy *Surgery*)

TRANVERSE COLON ESOPHAGOPLASTY

The arteries to the right side of the transverse colon are usually larger than those to the left side. For this reason, when a transplant is raised for a sufficient length to reach the neck, the isoperistaltic transplant (Figure 37-16A) affords a better blood supply than the antiperistaltic transplant (Figure 37-16B).

tioning transplant can be made by using a pedicle containing the inferior mesenteric and left colic arteries as the blood supply to the transplant, carrying the divided transverse colon to the neck. When the left part of the transverse colon and descending colon are used as a transplant, Rudler has recommended excising the right half of the colon and doing

supply, the excess ileum or ilcoecum is excised in the neck and an end-to-end anastomosis is made between the tip of the transplant and the cervical esophagus, using two to two and a half layers of carefully placed sutures of 00000 or 000000 silk. In order to make the anastomosis a large one, the cervical esophagus is slit in a longi-

in order to avoid pull on the anastomosis that occurs when the patient assumes an up-right position.

In the abdomen, the transverse colon, which has been drawn behind the stomach, is divided in an appropriate location so that it can be anastomosed as high in the stomach as is feasible. The lower end of the transplant is

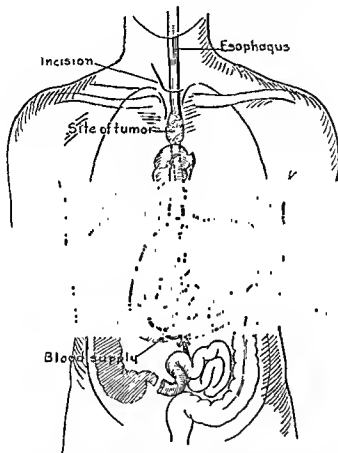


Fig. 37-14. Esophagoplasty using right ileocolic transplant. The transplant is passed posterior to the stomach, through the gastrohepatic ligament, and then through the substernal tunnel to the neck. Care is taken to avoid damaging the friable veins or causing venous thrombosis by too much tension. (From E. B. Mahoney and C. D. Sherman, Jr. [14], courtesy Surgery.)

tudinal direction slightly and if the ileum is used, it is also slit on the antemesenteric border for a short distance before making the anastomosis. If the cecum is used for anastomosis (the terminal ileum having been excised), it is preferable to make an incision into the cecum parallel to the entering blood supply to avoid transecting any vessels coming into the bowel. The cecum is sutured to the surrounding tissues in the neck. The patient is kept lying in bed for six or seven days

anastomosed to a suitable section of the anterior wall of the stomach with either one-layer or two-layer anastomosis. Bowel continuity is re-established by an end-to-end ileotransverse colostomy (Figure 37-15) consisting usually of a single layer of interrupted silk sutures. Heineke-Mikulicz pyloroplasty is done routinely because the stomach has been vagotomized. As a safety precaution and for feeding purposes, a gastrostomy is performed. The abdomen is closed in a routine manner.

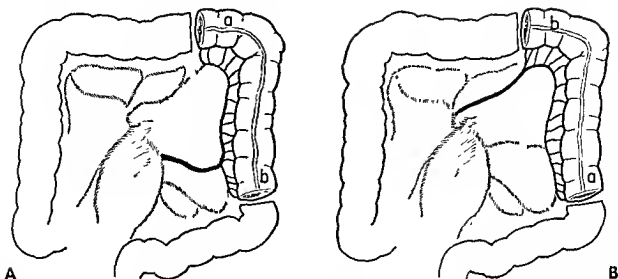


Fig. 37-17. Esophagoplastic using left colon transplant. A Isoperistaltic left colon transplant. This gives consistently the longest transplant of all bowel transplants and may prove to be the best one to use after cervical esophagectomy laryngectomy. As always, the collateral circulation should be tested by clamping prior to dividing the left branches of the middle colic artery. B. Antiperistaltic left colon transplant. This also consistently gives a long transplant but has the minor objection of being antiperistaltic.

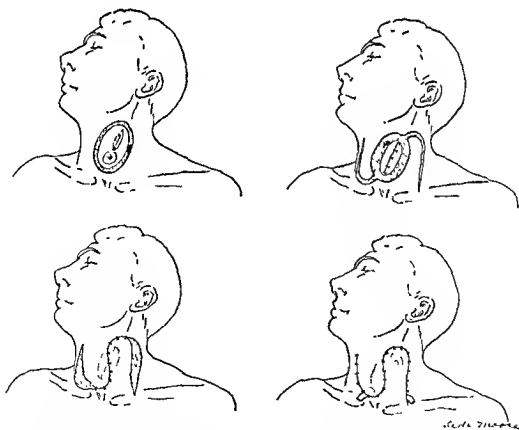


Fig. 37-18. Second stage plastic reconstruction after esophagectomy. Technic of delayed anastomosis of cervical esophagus either to jejunal or colonic stoma.

an ileosigmoidostomy rather than attempt to bring the remnant of the right half of the transverse colon down to the sigmoid and do an anastomosis to re-establish gastrointestinal continuity (Figure 37-17).

MISCELLANEOUS CONSIDERATIONS

IMMEDIATE RECONSTRUCTION

The most common method of immediate reconstruction constitutes an esophagogastr-

ISOPERISTALSIS VERSUS ANTIPERISTALSIS

Iso-peristalsis is the preferred method for effecting an anastomosis, especially when small bowel is used. One of us (C. D. S.) has shown by moving pictures that reverse peristalsis for esophageal replacement can be dangerous, and antiperistalsis may carry material placed in the stomach all the way to the pharynx. However, one of us (T. R. M.) has used antiperistaltic small bowel replacement with good results and has a number of pa-

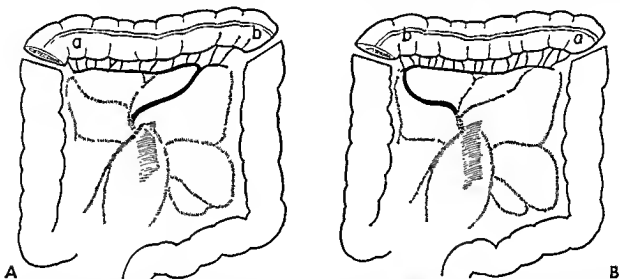


Fig. 37-16 Esophagoplasty using transverse colon. A. Iso-peristaltic transplant of transverse colon with arterial supply coming through arteries of the left side of the transverse colon. There is considerable variation in the quality of collateral circulation with this type of transplant, and testing by clamping the arteries of the right side is important before actual division of these vessels. If the blood supply is adequate, the isoperistaltic transplant is preferred over the antiperistaltic shown in B. B. Antiperistaltic transplant of transverse colon. The "right colic" artery gives a very good blood supply to this transplant, but the isoperistaltic transplant is preferred.

tomy (see Chap. 35). Other methods consist of the use of colon, jejunum, or a tube of stomach. Immediate reconstruction with organs other than stomach should not be done unless the patient's condition is good, inasmuch as the other methods of reconstruction readily lend themselves to a second-stage operation and the over-all mortality drops markedly with the two-stage procedure.

DELAYED RECONSTRUCTION

When the colon, jejunum, or stomach tube is used for delayed reconstruction of the esophagus, the second stage may take place from two weeks to six months following the primary procedure (Figure 37-18).

tients who are entirely asymptomatic from four to seven years after this procedure. Since the peristalsis of the colon is not as marked and the lumen is large, the direction of peristalsis is not very significant when the colon is used for replacing a removed esophagus.

ROUTE OF ASCENT OF THE TRANSPLANT

Inasmuch as the authors prefer a subtotal Torek type of esophagectomy, a cervical anastomosis is performed. Such an anastomosis is safe, for if there is a leak or breakdown, this is usually a minor complication, healing spontaneously, often without stricture. The safest and shortest route is through the substernal

Radiation Treatment of Esophageal Cancer

William L. Watson
and
John T. Goodner

Cancer of the esophagus may remain localized until death resulting from perforation of the esophagus. Post-mortem examination in 180 patients who died from esophageal cancer showed distant metastases in 76 (42 per cent) and bone metastases in 12 (6.6 per cent). Two patients with early esophageal cancer treated by protracted x-radiation died as a result of perforation of the esophagus followed by suppurative mediastinitis. At autopsy, no residual cancer or metastatic deposits were found. Thus, external irradiation may effect a complete destruction of localized esophageal cancer in a few instances.

The techniques and results of treating 782 patients by radiation therapy are presented in this chapter.

METHODS OF RADIATION THERAPY

The radiation treatment procedures are divided into five groups. The first group includes patients treated with external roentgen therapy by the protracted or fractionated dosage method. The second group was treated by gastrostomy and intracavitary radium element tandem. A third group includes patients treated first by gastrostomy and then by external irradiation followed by divided doses with the radium element tandem. The fourth group, composed of a small number of patients with cancer of the upper esophagus, was treated by surgical exposure of the cancer and the insertion of gold-filtered radon seeds directly into and about the tumor. A fifth method of treatment is "rotation x-ray

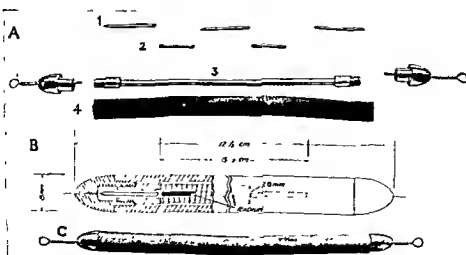


Fig. 38-1. The esophageal radium element tandem. A. Unassembled: 1, three radium element tubes of 10 mg. each; 2, two dummy tubes; 3, flat wire stainless steel tubing with nickel steel end pieces; 4, black rubber tubing. B. Mechanical drawing of tandem. C. Tandem assembled ready for use.

tunnel. Transplants have been made through the posterior mediastinum, in the right and left pleural cavities, both anterior and posterior to the lung, and subcutaneously, but are considered by the authors to be inferior to the substernal route. The substernal route places a transplant out of the path of x-ray beams which may be directed to the lymph nodes of the posterior mediastinum following esophageal resection for carcinoma, or to residual carcinoma when a palliative by-pass procedure has been performed. The substernal route is also ideally suited to the two-stage procedure since the chest does not have to be re-entered by formal thoracotomy in order to transport the transplant to the neck.

CERVICAL FISTULAS

This may occur when an ileocolic transplant is used but is not usually a serious problem. Transplants of colon, but more often of jejunum, may break down for a considerable distance owing to gangrene of the upper half of the loop. This complication is best treated by adequate drainage through a median sternotomy to the level of viable bowel. If the gangrenous segment is not too long, it may heal spontaneously; or it is occasionally possible at a later operation to mobilize the remaining colon or jejunum sufficiently so that a re-anastomosis can be performed.

CERVICAL ANASTOMOSIS AS A PALLIATIVE BY-PASS PROCEDURE IN INOPERABLE CANCER

A high percentage of inoperable carcinomas will perforate in the mediastinum or into the trachea, creating a tracheoesophageal fistula. For this reason, it is advisable when a palliative by-pass procedure is accomplished to divide the esophagus and invert the lower end, thereby avoiding drainage through such perforations. Scanlon believes that, when tumor of the esophagus extends into the cervical region, it is best simply to perform an end-to-side anastomosis. Neville [19] suggests that a catheter be placed in the distal open end of the esophagus and brought out laterally through the neck.

USE OF INERT MATERIALS IN ESOPHAGOPLASTY

Various stiff and pliable plastic and other inert materials have been used to bridge short defects to esophageal continuity, particularly following palliative resections simply to restore a lumen. Inert metal and plastic tubes have been introduced through an esophageal cancer to restore or maintain the lumen so that the patient could swallow. None of these procedures is recommended when there is a chance for cure. Occasionally they may seem to offer the best hope of maintaining a lumen, but in general there are other methods of palliation (resection, by-pass, irradiation) that are more useful.

mm.) esophagoscope is passed into the stomach, the gastric contents are aspirated, the organ is distended with air, and the olive-tipped bougie or string is picked up with biopsy forceps and brought out through the stoma (Figure 38-2). Stout shoemaker's twine is substituted for the silk and tied to the tandem, which is then passed through the gastrostomy stoma into the stomach and drawn upward into the esophagus to the lower level of the cancer. The oral end of the string is then passed through a regular adult esophagoscope, which in turn is inserted into the esophagus down to the tumor. By steady traction on the oral end of the string, the tandem

720 mg. hrs. (30 mg. for 24 hours)* has been delivered, the tandem is drawn upward and out through the mouth, a fresh length of string having been tied to the distal end and drawn through the stoma, to be used in reinserting the applicator for the next treatment.

The tandem is inserted every two days over a period of eight to twelve days, during which time a total of from 2,280 to 4,320 mg. hrs. is delivered to the tumor region. The patients do not complain of discomfort during treatments, and if the throat is well cocaineized and 1 per cent procaine is used to infiltrate the skin about the gastrostomy stoma before dilating it, they do not greatly

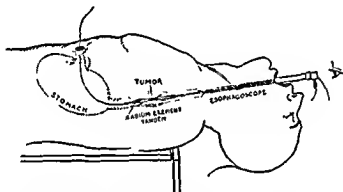


Fig. 38-3. The radium element tandem is pulled upward by steady traction until, under direct esophagosopic vision, the level of the esophageal cancer is reached

is pulled upward under direct vision until its proximal end is 3 cm. above the upper limits of the tumor (Figure 38-3).

The esophageal lumen is usually narrow and the tandem tends to be held firmly in position by the neoplastic stricture, but it is nevertheless anchored in place by fastening the proximal end of the string to a tooth and the distal end with adhesive tape to the anterior abdominal wall. The length of the proximal and distal ends is measured and these measurements are used in reinserting the tandem for the next treatment, thus eliminating the necessity for repeated endoscopic procedures. The tandem is left in position for 24 hours, during which time the patient expectorates his saliva and regular nutrition is maintained by gastrostomy feedings.

At the end of 24 hours, when a dose of

mind the original endoscopic procedure and initial insertion of the tandem.

Treatment by gastrostomy and intraesophageal irradiation with a special 30 mg. radium element tandem proved unsatisfactory. The applicator, with a total filtration equivalent to 2 mm. brass, was found to have a beneficial effect in lessening tumor infection, healing ulceration, and widening the lumen of the esophagus at the tumor site, but had apparently little effect on the main tumor mass.

Although radium is seldom used at present, the above technic would lend itself well to a

* Until recently, all expressions of interstitial radiation therapy consisted of the terms "milligram hours," when radium was used, and "millicurie hours," when radon was used. It would be impossible at this time to evaluate the tumor volumes that would be necessary to convert the above expressions into the at present acceptable term of "gamma roentgens."

therapy" (see Vol. I, Chap. 19, and Chap. 39, this volume).

Intraesophageal Radium Therapy

The radium tandem (Figure 38-1) is a moderately flexible rubber-covered applicator of flat, coiled, stainless spring steel gilly wire with smooth, blunt, nickel steel ends each with a loop of stainless steel wire to facilitate attachment of the shoemaker's twine used in manipulating and holding the tandem in its proper position in the esophagus. It has an over-all length of 12.5 cm., although it is well to have a second and shorter applicator for the treatment of small cancers and those just

its peroral extraction. The flat wire allows even radium filtration not possible when a round wire is used. This tubing is safe, is easily cleaned, and does not rust and cause difficulty in the removal of the radium needles. The inside diameter of the tube is 1.5 mm., sufficient to allow easy introduction of the radium element needles. The outside diameter is 8 mm.

Securely screwed to each end of the flat wire tube is a smooth, blunt-nosed, nickel silver piece that allows easy introduction, without trauma, through the gastrostomy stoma and also through the narrowed diseased portion of the esophagus. Anchored to each

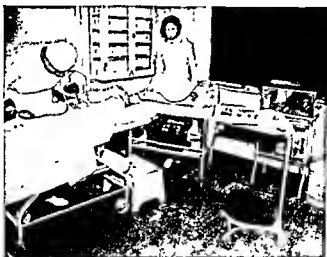


Fig 38-2 An olive-tipped bougie has been introduced into the stomach. After the gastrostomy stoma has been dilated, a small esophagoscope is inserted into the stomach and the bougie is picked up.

below the level of the cricopharyngeal constriction. The radiation is produced by three radium-element needles each of 10 mg. strength. These needles have a filter of 0.25 mm. platinum and the total filtration of the applicator is equivalent to 0.4 mm. platinum. The radiation is 98 per cent gamma and 2 per cent hard beta rays. It is possible to vary the position of the radium needles in the container and so concentrate the dose by the use of two dummy needles, as shown in Figure 38-1A.

The stainless steel tube of flat gilly wire is flexible enough to allow the tandem readily to be drawn through the gastrostomy stoma and past the angle at the junction of stomach and esophagus. Its flexibility also facilitates

of these end-pieces is a short, nickel silver wire with a terminal loop to which is attached the strong twine used in manipulating the tandem. A section of ordinary black rubber tubing 8 mm. in its outside diameter covers the flexible metal portions of the tandem.

The tandem is placed accurately in the esophagus at the level of the cancer by combined retrograde gastroscopy and esophagography. If the cancer will permit the passage of a small (7 mm.) olive-tipped bougie, this is done under direct vision; otherwise, the patient is given a black silk thread to swallow at the rate of a foot per hour for 24 hours. The gastrostomy stoma is dilated with graduated Hegar cervix dilators and a small (9

cision were found to be nonresectable. In two patients widespread infiltration and fixation were present, and in the other two patients extensive metastases to cervical lymph nodes were noted. After surgical exposure three of these patients had gold-filtered radon seeds inserted into and round about their cancers. This group offers the greatest opportunity to treat the cancer with adequate, concentrated, and localized dose of interstitial irradiation. The radiation sources can be placed into the

ing the tissues traversed by the direct roentgen-ray beam.

Other Forms of Therapy

The newer forms of radiation therapy include rotation therapy, telecobalt therapy, and betatron methods.

END RESULTS

During the years 1926-1957, 1,484 patients bearing cancer of the esophagus have been

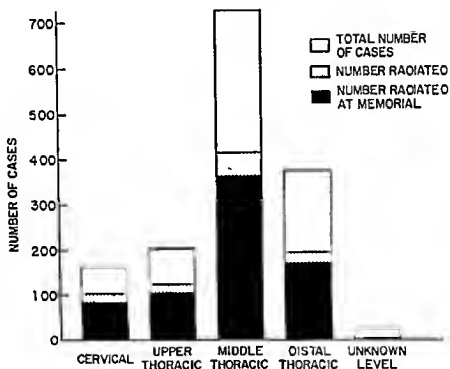


Fig. 38-6. The total number of patients with cancer of the esophagus, the distribution of the cancers, and the number treated with radiation therapy Memorial Hospital, 1926-1957 (see text).

tumor itself without going through an infected, ulcerated surface, as is necessary if the seeds are to be inserted through the esophagoscope.

External X-ray Therapy

Each patient was examined fluoroscopically in the position held during treatment and portals outlined under direct vision. Esophageal cancers have been treated through four portals, two anteriorly and two posteriorly, each measuring 7×14 cm. A final check is made by exposing a roentgen film to the beam from the 1,000 kv machine with the patient in position for treatment, thus outlin-

seen at Memorial Center; 165 cancers (11 per cent) were in the cervical esophagus, 201 (14 per cent) in the upper thoracic esophagus, 723 (49 per cent) in the midthoracic esophagus, and 373 (25 per cent) in the distal thoracic esophagus. There were 22 cases in which the level of the cancer was unknown (Figure 38-6).

Of the total number, 160 were not proved by biopsy or esophageal washings; thus, there were 1,324 proved cases of cancer of the esophagus. One hundred and four patients were lost to follow-up while still alive; therefore, there are 1,220 determinate cases in which to study survival.

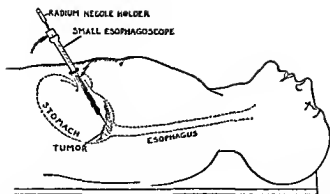


Fig. 38-4. The method of inserting gold-filtered radon seeds into cancer of the cardiac portion of the esophagus and stomach by means of a small esophagoscope inserted through the gastrostomy stoma.

suitable radioactive isotope for the inter-luminal treatment of esophageal cancer.

Interstitial Radium Therapy

If an esophageal cancer is to be treated by the insertion of radon seeds, it has been found a simple task with the aid of the esophagoscope to insert the radon seeds accurately into the upper two thirds of the tumor, but to plant radon seeds satisfactorily in the distal third of the cancer it is necessary to visualize that portion of the tumor by retrograde esophagoscopy through the gastrostomy stoma (Figures 38-4 and 38-5). Gold-filtered radon seeds, ranging in strength between 1.25 and 1.5 mc. each, have been found satisfactory.*

*EDITORIAL NOTE: Radioactive isotopes, such as those of gold, iridium, chromium, and others, may be used instead of gold-filtered radon seeds

Combined Gastrastomy, Raentgen Therapy, and Radium Therapy

Patients with complete esophageal obstruction were treated by gastrostomy to prevent death by starvation. Owing to the combination of gastrostomy and roentgen treatments, the lumen of the esophagus became patent and a radium element tandem was inserted without undue trauma.

Surgical Exposure and Interstitial Irradiation of Cancer of the Cervical Esophagus

In this group are a small number of cancers that occurred in that portion of the esophagus from the piriform sinuses to the level of the thoracic inlet. These patients theoretically have operable cancers, but four such cancers exposed through a cervical in-

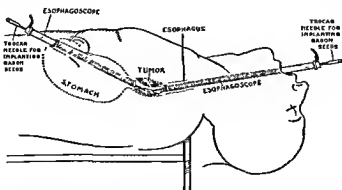


Fig. 38-5. Implanting gold-filtered radon seeds into an esophageal cancer. Two esophagoscopes are used in order to visualize both proximal and distal margins of the cancer.

Radiation Treatment of Esophageal Cancer

hrs. measured in air and lived 15 months after therapy. The range of dose for all patients was 14,000 to 208,000 mc. hrs., with a median of 113,000 mc. hrs. The applicator was a 4-Gm. radium element pack usually applied at a radium-skin distance of 20 cm. There were 9 patients in whom some other form of irradiation was used in combination with the radium pack, with little change in effect as the average survival for the latter group was 4.9 months.

RADIUM TANDEM

Thirty-one patients were treated with a radium applicator introduced into the esopha-

ROENTGEN THERAPY WITH LESS THAN 198 KV

This is a heterogeneous group in which there was a variation of treatment from 90 to 195 kv. During the years 1926 and 1927 a 90 kv roentgen machine was used. The intermediate kilovoltage was used from 1928 until 1930 when use of 198 kv apparatus was started. There were 47 patients in this group, with an average survival of 4.4 months. The dosages are unknown, as only the number of treatments was recorded during the early period; these varied from 1 to 14 treatments, and the patient with the longest survival (14

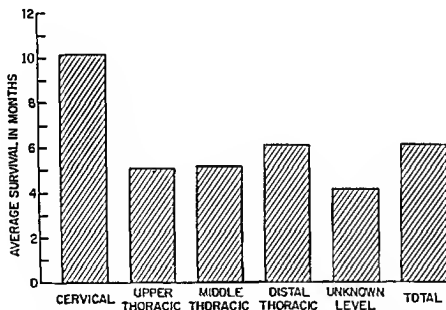


Fig. 38-7. Average survival in months of patients with cancer of the esophagus treated with roentgen therapy (1926-1957), comparing the survival in relation to the level of the cancer.

gus, 10 of whom were treated by this method exclusively. For these 10 patients the average survival was 4 months, the longest survival being 10 months. Dosage ranged from 1,200 to 4,500 mc. hrs., with a median of 2,850 mc. hrs. The other 21 patients were treated with some other form of radiation in combination (1 with 1,000 kv; 5 with 250 kv; 13 with 198-200 kv; 1 with radium element pack; 1 with 90 kv). In this group treated by combined therapy, the longest survival was 23 months and the average was 6.2 months. This indicates that the added therapy improved the survival when compared to the use of the radium tandem as the only form of radiation therapy.

months) received the most treatments (14). Seven patients were treated with either radium tandem or radium element pack in combination with the roentgen therapy, with an average survival of 5 months. Five patients treated with radium element pack in addition to the x-ray survived an average of 6.4 months.

ROENTGEN THERAPY WITH 198-200 KV

The number of patients treated by this method totaled 194, with an average survival of 7.7 months. There were 2 long survivors in this group. One, with a Grade II squamous carcinoma of the cervical esophagus, received an air dose of 2,500 r and survived 10 years

TABLE 38-1.—NUMBER OF CASES OF CANCER OF THE ESOPHAGUS (727) TREATED BY RADIATION THERAPY ALONE (1926-1957)

	<i>Cervical</i>	<i>Upper third</i>	<i>Middle third</i>	<i>Distal third</i>	<i>Unknown location</i>	<i>Total</i>
Betatron therapy	2	0	0	0	0	2
Cobalt teletherapy	3	7	18	4	0	32
1,000 kv roentgen therapy	13	41	126	41	2	223
250 kv rotation therapy	0	10	40	6	0	56
250 kv roentgen therapy	35	17	51	22	0	125
198-200 kv roentgen therapy	24	15	88	67	0	194
Less than 198 kv roentgen therapy	0	7	24	15	1	47
Radium pack teletherapy	7	8	9	9	0	33
Intraesophageal radium tandem	0	1	5	4	0	10
Interstitial radon seeds	0	0	2	3	0	5
Total	84	106	363	171	3	727

One hundred and thirty-two patients were treated by surgical methods exclusively and 245 received no treatment, leaving 843 patients who received radiation therapy. Of these, 61 were irradiated elsewhere. Fifty-five patients were treated by combined resection and irradiation; the remaining 727 were treated by radiation therapy alone (Table 38-1).

RADON SEED IMPLANTATION

There were five patients in whom the intraesophageal insertion of radon seeds into the tumor was the only form of therapy. The average survival was 9.2 months (Table 38-2). The dosage of seed implantation varied from 1,330 to 2,931 mc. hrs., with a median of 2,130 mc. hrs. In addition, there were 29 patients in whom the intraesophageal tumor implantation was accompanied by 198-200 kv

external x-irradiation. In these cases, the range of dose was 346 to 8,903 mc. hrs., with a median of 4,625 mc. hrs. The average survival following the radon seed implantation was 6 months, whereas the average survival following the x-ray therapy given in combination was 11 months. Interstitial irradiation was first used in 1934 but has been used only on rare occasions since 1940. It was abandoned because of the high incidence of esophageal perforation.

RADIUM ELEMENT TELETHERAPY

This form of therapy was used between 1926 and 1940, with a total of 33 patients being treated. The average survival was 4.7 months (Figure 38-8). The patient who survived longest was one with a Grade II squamous carcinoma of the midthoracic esophagus who received a dose of 80,000 mc.

TABLE 38-2.—AVERAGE SURVIVAL IN MONTHS OF PATIENTS WITH CANCER OF THE ESOPHAGUS TREATED BY RADIATION THERAPY (1926-1957)

	<i>Cervical</i>	<i>Upper third</i>	<i>Middle third</i>	<i>Distal third</i>	<i>Unknown location</i>	<i>Total</i>
Betatron therapy	8.5	—	—	—	—	8.5
Cobalt teletherapy	10.3	6.8	5.0	3.5	—	5.7
1,000 kv roentgen therapy	10.2	6.4	6.3	6.0	4.0	6.5
250 kv rotation therapy	—	4.8	2.1	5.6	—	4.7
250 kv roentgen therapy	8.4	4.8	4.8	9.7	—	6.4
Less than 198 kv roentgen therapy	16.9	5.1	6.1	7.2	—	7.7
Radium pack teletherapy	—	2.9	3.9	5.7	6.0	4.4
Intraesophageal radium tandem	4.6	4.1	5.0	5.0	—	4.7
Interstitial radon seeds	—	3.0	4.8	3.2	—	4.0
Total	10.9	5.3	5.5	6.8	4.7	6.4

average survival of 6.4 months. Included was a patient with a Grade I squamous carcinoma of the cervical esophagus who survived 5 years and 8 months after irradiation (7,350 r air dose). The air dose varied from 300 to 32,400 r, with a median of 16,350 r. The radiation factors consisted of 30 ma., 1.5 mm. Cu filtration, 2 mm. h.v.l., T.-S.D., 50-70 cm. The tumor dose was calculated in only 16 cases and in these the range of dosage was 720 to 5,980 r, with a median of 3,350 r. In this group there were 5 patients who received supplemental radiation with another modality: 1 of these also received intraesophageal interstitial irradiation and survived 3 months; 4 were treated with a radium tandem in addition, but the average survival (6.8 months) was not much different from that of patients receiving 250 kv therapy alone.

250 KV ROENTGEN ROTATION THERAPY

Fifty-six patients were treated by 250 kv roentgen rotation therapy, with an average survival of 4.7 months. The range of dosage (tumor dose) was from 634 to 14,456 r, with a median tumor dose of 7,545 r. The longest survival was 14 months. One patient is still alive over 5 years, she is an eighty-year-old female (seventy-five years when treatment was given) with a Grade II squamous carcinoma of the distal esophagus who received a tumor dose of 7,000 r by rotation therapy, but in addition had a radium applicator inserted into the esophagus on three occasions with a total of 901 mc. hrs.

1,000 KV ROENTGEN THERAPY

In this group there were 223 patients, with an average survival of 6.5 months. The range of dosage varied from 300 to 22,700 r in air, with a varying tumor dose of 1,629 to 9,507 r. The median air dose was 11,500 r and the median tumor dose 5,568 r. One patient in this group survived slightly less than 7 years.

He had a Grade III squamous carcinoma of the midthoracic esophagus and received an air dose of 11,200 r. (See also Chap. 40.)

TELECObALT THERAPY

Thirty-two patients comprised this group. The largest number of cancers (18) were in the midthoracic esophagus. The average survival was 5.7 months. Eight patients were treated with telecobalt in combination with some other form of therapy, the average survival being 6 months. For the 24 patients treated by telecobalt alone, the survival averaged 5.7 months, the same as for the entire group. Thus, statistically there was little difference in survival whether they were treated with telecobalt alone or in combination with some other form of irradiation. The dosage range (tumor dose) was 1,400 r to 7,200 r, with a median tumor dose of 4,300 r. The longest survival was a seventy-year-old white female with a Grade III squamous carcinoma of the cervical esophagus who received a tumor dose of 5,000 r and lived 32 months.

BETATRON THERAPY (22 MEV)

There have been only three patients treated by this method—not significant for statistical analysis. All had cancer of the cervical esophagus. One patient, who was also treated with an intraesophageal iridium nylon thread, is still alive. One of the other patients was also treated by telecobalt therapy elsewhere (4,500 r) and survived one year. The average survival of the two patients who have expired was 8.5 months.

TOTAL RADIATION EXPERIENCE

The over-all average survival for the 727 patients who received radiation therapy alone is 6.4 months. From 1926 to 1953, there were 672 patients treated by irradiation, with 7 survivals of 5 years or more—a 5-year survival rate of 1 per cent (Figure 38-8).

and 8 months. The other, with the same type of cancer, received an air dose of 6,300 r and survived 11 years and 8 months. Both were treated with a 200 kv x-ray machine, the factors being 30 ma., 70 cm. T.-S.D., 0.5 mm. Cu filtration. The dosage in these 194 cases ranged from 400 to 24,000 r in air, with a median of 12,200 r.

with a radium tandem in addition to the x-ray survived an average of 7.3 months. There was 1 patient who received radium element pack therapy and 1 treated with a radium tandem and intracosophageal radon seeds with the x-ray therapy; each survived only 4 months.

Of the remaining 155 patients who received this type of x-ray therapy exclusively, the

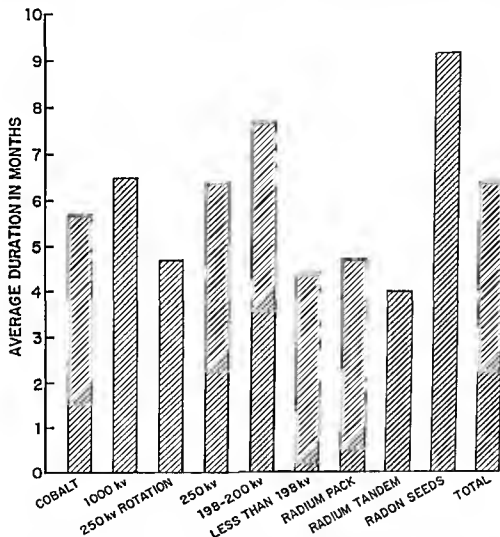


Fig. 38-8. Average survival in months of patients with esophageal cancer treated with radiation therapy (1926-1957), comparing the survival in relation to the technic of irradiation employed.

There were 39 patients who received some other form of radiation therapy in combination with the x-ray; this consisted of either intracosophageal radon seeds, radium tandem, or radium element pack. The average survival in this subgroup was 9.8 months. Twenty-five patients received x-ray and intracosophageal radon seeds, with an average survival of 11.5 months; whereas 12 patients who were treated

average survival was 7.4 months. There was not much difference in the average survival between those who received the x-ray treatment alone and those who had treatment with a radium tandem in addition.

250 KV ROENTGEN THERAPY

One hundred and twenty-five patients were treated by 250 kv roentgen therapy, with an

The main objective in rotation therapy is to obtain the best ratio between the roentgen dose in the central core and that on the surface. This desideratum will be best favored under the following conditions:

1. The diameter of the body should be small to favor the depth dose.

surface intensity at 100 per cent); with a gap of 3 cm., 269 per cent; and with a 4 cm. gap, only 229 per cent, other premises unaltered.

3. In rotation therapy the shorter the focal distance, the greater the divergence of the roentgen beam, and accordingly the greater



Fig. 39-1. Apparatus for roentgen rotation therapy



Fig. 39-2. Fluorescent screen with special arrangements

2. The incidence field or, more exactly, the width should be small, increasing the difference in radiation time between superficial layers and center. The diaphragm, therefore, should remain as narrow as possible regarding the size of the core to be irradiated. The significance of the diaphragm width is apparent from the measurements made by Nakaidzumi and Miyakawa [33] on rotating phantoms. With a diaphragm gap of 2 cm., these workers obtained a central dose of 334 per cent (the

the difference in irradiation time between skin and center is noted.

4. *Roentgen penetration and filtration.* The difference in central intensity is relatively slight with variations in voltage, and with certain limits with different filtrations [33]. However, when thin or no filters were used, skin reactions were severe in patients with esophageal cancer that required a high central dose. This feature may limit continued treatment. Accordingly, filters of 0.5 mm. Cu + 1 mm.

Rotation Roentgen Therapy of Esophageal Cancer

*Bertil Ebenius,
Lars Edling,
and
Inge Gynning*

APPARATUS AND GENERAL CONSIDERATIONS

Roentgen rotation therapy has been developed in the past fifteen years and is a method for improving the technical efficiency in treating deeply situated malignant tumors. It is discussed in detail in Volume I, Chapter 19. A description of the apparatus of the King Gustaf V Jubilee Clinic in Lund, Sweden, and its use in treating cancer of the esophagus are presented here.

This apparatus is intended for treatment with a beam perpendicular to the longitudinal axis of the patient.

The apparatus itself (Figure 39-1) is a wooden chair with a vertical back and adjustable head support placed upon a circular platform, movable on double ball bearings in two directions at right angles to one another. This platform is rotated by an electric motor. The complete apparatus may be moved on rails in the floor for modifying the focal distance. The roentgen tank, of Siemens' model, likewise is adjustable in every direction by set screws. It is provided with a slit diaphragm that may be regulated by Bowden cables from the control room and must be supported to the wall, floor, and roof to prevent uncontrolled displacements.

The adjustment of the width of the roentgen beam as well as the object in relation to the roentgen center is set from the control room by means of a fluorescent screen. The fluorescent image is necessary in controlling the posi-

tion of the object during the treatments. The size of the field is controlled on the screen by movable rubber strings marking the limits of the field, plus its vertical and horizontal midline (Figure 39-2).

Experience has taught the advantage of using a fixed focal distance of 53 cm. During the treatment, the therapy room as well as the control room must be dark. An effective air conditioning is a matter of importance for both rooms.

The theory of the rotation method and its use in practice are based on the fact that the core, toward which the roentgen beam is directed, will be exposed to continuous treatment, while each point of the skin surface will receive irradiation for a fraction of that time only.

DuMesnil de Rochemont [24] calculated mathematically curves for depth and surface at each point of the object hit by the beam. Figure 39-3, a schematic figure borrowed from his work, demonstrates the geometric conditions to be considered in rotation therapy.

As an illustrative example, a curve is reproduced in the treatment of esophageal cancer with 180 kV and a depth dose of 30 per cent at 10 cm. (Figure 39-4) [24]. Here the intensity, being limited on the surface to 50 per cent, keeps fairly constant in the next 7 to 8 cm. depth, but then rises suddenly, reaching as high as 130 per cent in the rotation center.

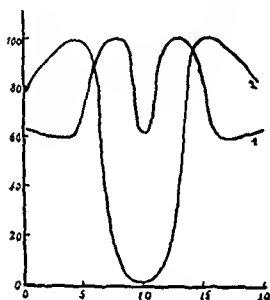


Fig. 39-5. Intensity curves after displacement 2 cm. and 5 cm. out of rotation center. (From Nielsen)

Al have since been used with gratifying results as pertains to skin reaction.

5. The volume dose will decrease with stationary fields as with rotation when the

incidence field is diminished. With stationary fields, the back-scatter will decrease, along with percentage depth dose. With rotation therapy, the back-scatter is not as important for the total dose as is the width of the field. By narrowing the field, the volume of irradiated tissue is not reduced, but the volume dose is decreased owing to the shortening of irradiation time per unit volume.

Stationary fields with a relatively small tissue volume, but a high volume dose in superficial layers, must involve more risk of superficial tissue damage than a rotation treatment. The incidence field may be wide enough to cover the whole tumor plus regional metastases.

6. The centering of the roentgen beam upon the central core must be exact, the smallest deviation bringing the most unfavorable consequences as to the distribution of roentgen intensity in the body. The curves in Figure 39-5 [39] show that a displacement of 2 to 5 cm. from the rotation center involves a very undesirable increase in in-

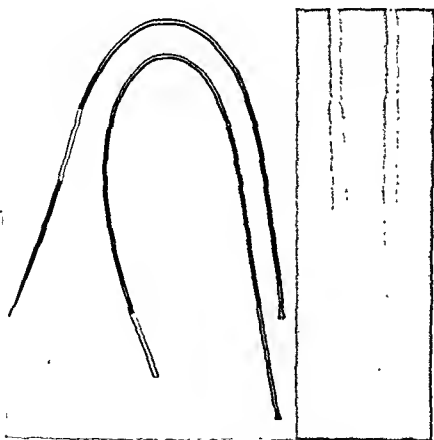


Fig. 39-6. Baugies for measurement of the tumor dose.

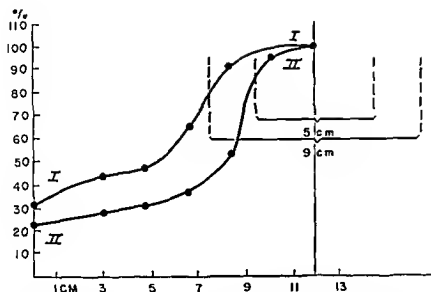


Fig. 39-9. Thorax phantom, level of cardia. 170 kv, 7 ma., $\frac{1}{2}$ Cu + 1 Al, focus, rotation center = 70 cm; focus, skin max. = 57 cm; focus, skin min. = 55 cm. Field in rotation center. Curve I, 9×12 cm; Curve II, 5×7 cm.

The purely mathematical determination used by duMesnil de Rochemont [24] is very schematic, which involves risks in applying the data to an individual case, for the exact place of the core is not always easily ascertained. An approach to clinical reality has been attempted by preparing phantoms imitating anatomic conditions as described by Nielsen [39]. These phantoms were designed especially for esophageal cancers. The thoracic skeleton of an adult man is used, covered externally by a layer of beeswax, corresponding to the form and thickness of the real

integuments. Within its cavity was attached a wax lump imitating the heart. Mediastinum, liver, and spleen were modeled in their respective places. The lung tissue was represented by a tightly packed cellular substance ("Zellstoff"), giving the proper contrast in screening. The existence of the real skeleton parts contributes in giving this phantom a relatively true absorption capacity.

In each phantom there was attached by wax a series of Sievert condenser chambers, placed in borings within an oblong paraffin block along the sagittal plane. Two positions for

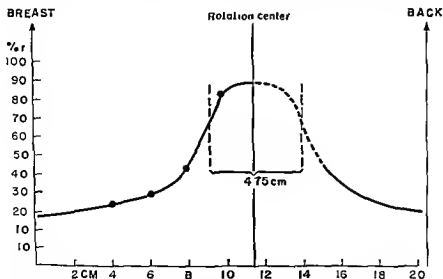


Fig. 39-10. Thorax phantom, level of bifurcation. 116 kv, 15 ma., $\frac{1}{2}$ Cu + 1 Al; focus, rotation center = 50 cm; field in rotation center = 4.75×14 cm.



Fig. 39-7. The bougie in the esophagus.

tensity in the surrounding normal tissues, whereas the intensity in the core itself will fall catastrophically. The deformation of the intensity curve increases with the displacement of the central ray.

7. The size of the central roentgen dose in rotation therapy, being no longer limited by

the skin tolerance, must of necessity be used with the utmost caution to prevent central radiation injuries that might possibly prove fatal. The safest method, which has routinely been followed in Lund, is to decide on the total tumor dose proved eligible by experience and gradually to approach it by daily fractionation. The daily dose or the daily time of treatment can be determined mathematically or by experimental irradiation of a phantom. Experience here has taught that the most exact dosage can be obtained only by individual measurement of the intensity in the central core by means of ionization chambers, if the circumstances will permit introduction in the right place. For this purpose, special equipment has been constructed (Figure 39-6). A capsule of aluminum mounted on the esophageal bougie contains two Sievert ionization chambers. Pieces of lead above and below the chambers make the location of these visible on the fluorescent screen (Figure 39-7). After five or six measurements during the course of treatment, it is possible to estimate a relatively exact dosage with the treatments being carried out under similar conditions of focal distance, size of the field, etc. Since 1948 bougies with eight ionization chambers have been used, which is suitable for measuring the great difference that exists between the maximum and the minimum tumor dose.

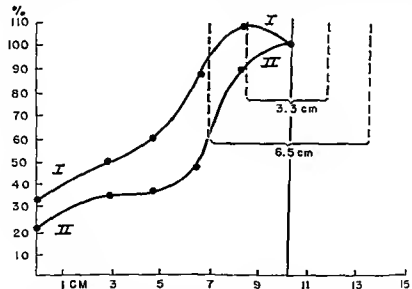


Fig. 39-8. Thorax phantom, level of bifurcation, 170 kv, 7 ma, 1/2 Cu + 1 Al, focus, rotation center = 70 cm; focus, skin max. = 59 cm; focus, skin min. = 52 cm. Field in rotation center: Curve I, 6.5 X 10 cm; Curve II, 3.3 X 12 cm.

actions in the esophagus and surrounding pulmonary tissue occur rarely.

The radiation effect on the tumor is generally noticeable a week after treatment is started, as evidenced by diminution of dysphagia. At the end of the radiologic treatment, none or only small remnants of the tumor are demonstrable roentgenologically. Stricture may appear after healing of the cancer, and in pronounced cases cautious bouginage becomes necessary.

The patient's general condition is only slightly influenced by rotation therapy, which therefore also may be given to very old and weak patients. Radiation sickness during the treatment occurs only exceptionally.

Determinations of the size of the field, using the roentgenologic findings, must include a "tumor free" margin of 2 or 3 cm. outside the visible limits of the tumor. Subepithelial growth as well as metastases close to the cancer is not always visible in the x-ray picture. The adjustment of the tumor in relation to the rotation center is carried out in frontal and sagittal direction. The rotation rate is chosen so the rotation stops with the chair in the same position as at the beginning of the

treatment, in order to get the desired complete revolutions.

RESULTS

The primary results in the treatment of esophageal carcinoma at Lund follow: From October 1943 to October 1949, 119 patients (70 men and 49 women) were treated. Ten patients died during the course of treatment. In 4 cases the treatment had to be discontinued on account of the debilitated condition of the patients. The treatment was completed in 105 patients. Distinct improvement was noted in 89, but only 64 were recorded as completely free of signs; 20 of the remaining 41 patients had roentgenologic changes indicative of a persistent tumor. Signs of ulceration in the esophagus within the tumor region were seen in 23 cases; 3 of these healed after gastrostomy, which was later closed. The calculated maximum total dose in these cases was between 6,250 r and 7,050 r per 35 days. Possibly the actual dose was higher.

In three cases no microscopic diagnosis, for some reason or another, could be obtained. The roentgenologic diagnosis in these cases was unmistakable, however. Two patients died



Fig. 39-12. (Left) Esophagogram of a 62-year-old female who had extensive carcinoma involving the mid-thoracic esophagus, treated with rotation radiation therapy. (Right) Roentgenogram of esophagus three years and four months after beginning of treatment. Tumor dose 6,100 r/36 days.

measurement were used along the course of the esophagus, namely, at the level of the tracheal bifurcation and of the cardia. The rotation center was marked by a small lead shot.

Figures 31-8 and 31-9 demonstrate some of the curves measured according to these conditions at a focal distance of 65 and 50 cm. from the rotation center:

a. At the level of bifurcation of the trachea (Figure 39-8).

Curve I. With a field width of 6.5 cm., applicable in many cases of esophageal cancer, the surface dose is only 35 per cent, the intensity in the rotation center being 100 per cent.

Curve II. With the extremely narrow field of 3.3 cm., the surface intensity decreases to 22 per cent. With Curve I, the maximum intensity lies a little in front of the rotation axis owing to absorption by the vertebral column, which is more conspicuous in the broader field.

b. At the level of the cardia (Figure 39-9).

The curves here show similar results in the percentage surface intensity. Curve I, with a field of 9×12 cm., corresponds well to practical conditions in esophageal cancer at this level, where the esophagus has a somewhat oblique course and requires a relatively broad field. Curve II has been taken as a contrast to the former.

The above curves refer to a focal distance of 65 cm, but similar measurements have been made using 50 cm. as the distance from

focus to rotation center. Such curves, reproduced in Figures 39-10 and 39-11, show the advantage in rotation therapy of shortening this distance. With a field of 4.75 cm. width, the surface dose is reduced to 26 per cent, whereas with a 6.6 cm. field it is reduced to 39 per cent, other conditions being unaltered.

TREATMENT OF ESOPHAGEAL CANCER

In the first years, a total tumor dose of 5,000 r in 20 to 35 days was used. All these patients died of local recurrence within one year. The total dose has been successively increased since 1944, all patients receiving more than 6,000 r in 30 to 40 days. The influence of the time factor has been determined following calculations of Strandqvist [43] and reported by Ahlbom [1]. Generally, a maximum tumor dose of 6,000 r in 35 days is required for clinical improvement lasting more than one year. Treatment is given 6 days a week, the daily tumor dose being about 200 r. Too large a daily dose risks perforation and mediastinitis. (The limit of intolerance of the thoracic tissues corresponds to a total dose of 7,100 r in 40 days, 6,900 r in 35 days, or 6,700 r in 30 days.)

Using a relatively narrow field, the skin reaction following such doses is remarkably slight, manifested by erythema, pigmentation, and scaling. Exudative epidermitis does not appear. As mentioned before, the width of the field and the thoracic diameter influence the intensity of reaction. Pronounced re-

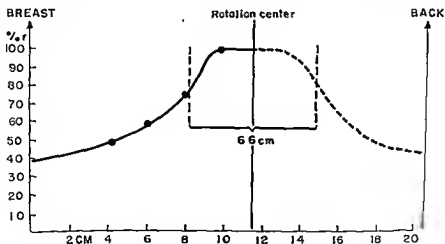


Fig. 39-11. Thorax phantom, level of bifurcation. 116 kv, 15 ma., $\frac{1}{2}$ Cu + 1 Al; focus, rotation center = 50 cm; field in rotation center = 6.6×10.7 cm.

actions in the esophagus and surrounding pulmonary tissue occur rarely.

The radiation effect on the tumor is generally noticeable a week after treatment is started, as evidenced by diminution of dysphagia. At the end of the radiologic treatment, none or only small remnants of the tumor are demonstrable roentgenologically. Stricture may appear after healing of the cancer, and in pronounced cases cautious bouginage becomes necessary.

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Fig. 39-12. (Left) Esophagogram of a 62-year-old female who had extensive carcinoma involving the midthoracic esophagus, treated with rotation radiation therapy. (Right) Roentgenogram of esophagus three years and four months after beginning of treatment. Tumor dose 6,100 r/36 days.



Fig. 39-13. (Left) Esophagogram of male, 79 years old, with extensive carcinoma of the thoracic esophagus. (Right) Roentgenogram of esophagus two years and nine months after beginning of treatment. Tumor dose 6,000 r/32 days.



Fig. 39-14. (Left) Esophagogram of male, 70 years old, with an infiltrating carcinoma of the midthoracic esophagus. (Right) Roentgenogram of esophagus two years and one month after beginning of treatment. Tumor dose 6,600 r/28 days.

TABLE 39-1.—ROTATION ROENTGEN THERAPY OF ESOPHAGEAL CANCER:
SUMMARY OF DEFINITIVE CURES FOR THREE OR MORE YEARS*

Number	Sex	Age	Length of tumor, cm.	Location of tumor	Daily tumor dose r/min.	Total tumor dose r/days	Corre- sponding dose/35 days†	Period of observation without local recurrence		Stricture	Remarks
								Years	months		
1	Female	62	7.5	Middle	210/15	6,100/36	6,100/35	8	8	0	Living
2	Male	70	8	Middle	275/15	6,600/28	6,900	7	4	Moderate	Living
3	Female	68	10	Middle	215/18	6,550/36	6,500	7	2	Total	Gastric fistula, living
4	Male	62	4	Middle	204/14	6,700/39	6,500	5	4	Marked	Rotated 240°‡ living
5	Male	72	5	Middle	200/10	6,440/33	6,500	5	0	0	Living
6	Female	64	7	Middle	205/7	6,600/41	6,300	4	4	Marked	Living
7	Male	70	5	Upper	200/13	6,100/36	6,100	3	8	0	Living
8	Female	72	5	Lower	210/10	6,350/38	6,200	3	6	0	Living. Tbc. pulm. Skeletal metast.
9	Male	65	8	Middle	230/8	6,550/36	6,500	3	5	Moderate	Living‡
10	Female	59	6	Middle	250/20	6,500/35	6,500	6	0	Marked	Died from inter- current disease, No autopsy
11	Male	79	5	Lower	230/18	6,000/32	6,100	5	6	0	Died at age 85. No local recur- rence. No au- topsy
12	Male	68	5	Lower	235/18	6,500/35	6,500	3	5	0	Probably died from cardiac disease. No au- topsy
13	Male	68	7	Upper	250/25	6,500/36	6,500	3	1	0	Died from me- tastases to supra- clavicular region and lungs. No local recurrence. Autopsy

* On July 1, 1956, 3 of 13 patients were still symptom-free. Three had been symptom-free for 10 to 12 years, 6 for 5 to 7 years, and 4 for 3 to 4 years.

† According to Strandqvist's diagram of fractionation.

‡ Irradiation ulcer. Healed after gastrostomy.

TABLE 39-2.—ROTATION ROENTGEN THERAPY OF ESOPHAGEAL CANCER:
LOCAL RECURRENCES

Group	I <6,000 r 35 days	II 6,000-6,400 r 35 days	III >6,400 r 35 days
Probable local recurrence	13	22	32
No signs of local recurrence			
Alive and symptom-free 1/10 1952	—	2	6
Living with metastases	—	1	—
Died from intercurrent disease	—	2	5
Died from overdosage complications	—	2	7
Died from metastases	1	6	6
Number of cases	14	35	56

comparatively soon after the completion of the treatment. All the other cases were verified microscopically.

In order to evaluate the results in relationship to the total tumor dose given during a certain period, the material is divided into three groups on the basis of Strandqvist's diagram of fractionation for radiation therapy of carcinoma of the skio. Group II represents cases corresponding to the mean value of the healing dose \pm 200 r, and Groups I and III cases in which the dose is lower and higher, respectively. It appears from Table 39-2 that the number of local recurrences is larger in Group I than in Groups II and III. These

facts support the view that most carcinomas of the esophagus require a tumor dose of the magnitude mentioned above if healing is to be attained.

The thirteen cases of at least three years' cure are of particular interest (Table 39-1). The occurrence of strictures may be due to the high dosage, though other factors may also be important.

Figures 39-12 through 39-15 show the roentgenologic findings in several cases before and after the treatment.

Concerning other methods of roentgenotherapy with a movable beam, the reader is referred to Volume I, Chapter 19.

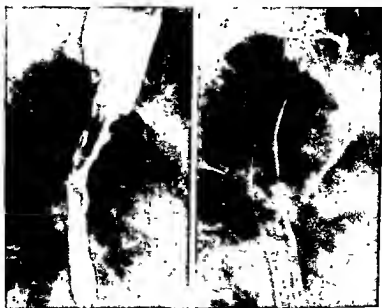


Fig. 39-15. (Left) Esophagogram of male, 68 years old, with carcinoma of the thoracic esophagus which had produced obstruction and proximal dilatation. (Right) Roentgenogram of esophagus one year and eight months after beginning of treatment. Tumor dose 6,500 r/36 days.

High-Energy Radiation Treatment of Esophageal Cancer

*Milton Friedman,
John W. Egan,
and
Martha E. Southard*

Prior to 1940, four problems had to be dealt with in the irradiation of carcinoma of the esophagus: (1) The required tumor lethal dose was large, ranging from 5,000 to 6,000 rads. (2) The large distance that the x-ray beam must traverse, from the chest wall to the esophagus, attenuated the beam so that a relatively small proportion reached the tumor. (3) The lung tissue traversed by the beam of x-rays was particularly vulnerable to serious irradiation injury from doses smaller than that necessary to destroy carcinoma of the esophagus. (4) The tumor was situated in a delicate, hollow viscus which, weakened by the initial erosion of the growth and the subsequent partial devitalization by irradiation, was in a poor condition for repair of the residual defect after the neoplasm had been destroyed.

Early in the 1940's several investigators [9, 12, 13] improved rotation technics so that some of the above-mentioned obstacles could be overcome (see Chap. 39). With rotation technic the irradiation was far more efficient, both theoretically and by physical measurements, in that a large dose could be delivered to the tumor without unduly injuring the intervening lung or skin.

With the increasing use of supervoltage (1 and 2 million volt) x-ray apparatuses, commencing about 1943, and of betatrons up to 22 mev and cobalt-60 teletherapy machines of different designs, it became a simple matter to deliver large doses of radiation to the

esophagus while relatively small doses were delivered to the adjacent normal tissues.

PHYSICAL PRINCIPLES OF HIGH-ENERGY IRRADIATION

The goal of efficient irradiation is to deliver a high dose to the tumor-bearing region and a low dose to adjacent normal tissues.

The administration of a lethal tumor dose through a single treatment field with x-ray machines operating in the energy range from 180 kv to 250 kv is limited by the tolerance of the surface of the skin. Consequently, multiple cross-firing portals, converging to a focal point in the tumor, had to be employed to deliver a substantial dose to a region deep in the body.

With the development of 1 to 2 mev x-ray machines and cobalt-60 teletherapy machines, the maximum surface dose through a single field was shifted to a depth of 3 to 4 mm. below the surface, thereby sparing the skin. Consequently, the early skin reactions were mild. The greater penetrability of the rays permitted large doses to be delivered through each skin portal without obvious initial damage.

It later became apparent that, when large skin doses (higher than 4,000 or 5,000 rads) were delivered through a single portal, the surface reactions several years after irradiation were severe. Dense subcutaneous fibrosis led to pigment changes, contracture, fixation, and

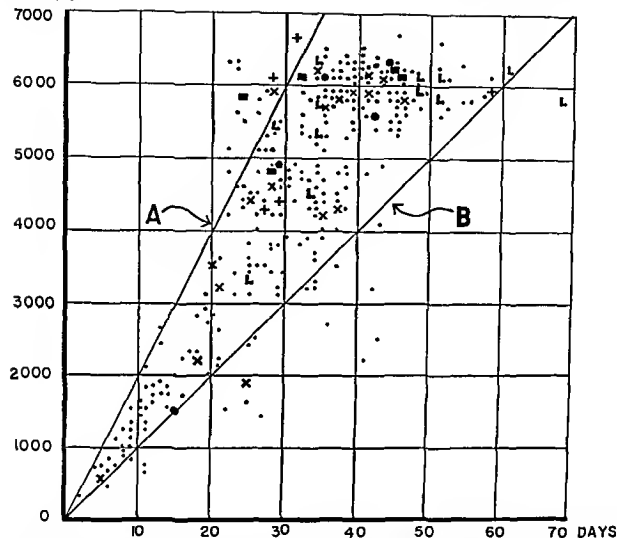
TUMOR
DOSE (r)

Fig. 40-1. Scatter diagram showing the relationship of tumor dose and treatment time to the results and complications in 296 cases of carcinoma of the esophagus treated by 190 kv radiation. The diagonal lines, A and B, represent tumor doses of 100 r per day and 200 r per day, respectively. The symbols used are: large square, apparent arrest for 2 years; large dot, apparent arrest for 1 year; L, living 18 months; small dot, dead of cancer; X, complication; +, hemorrhage. Note that the five cases arrested for 2 years received a tumor dose of from 5,000 r to 6,000 r. These results are typical of the best that could be achieved with orthovoltage technics. Note also that within this same tumor lethal dose range the highest number of complications occurred. (Redrawn from Kahler.)

even necrosis of the skin and subcutaneous tissues.

Various severe radiation injuries of deep structures were also encountered in the thorax, such as severe radiation pneumonitis, damage to the spinal cord, and dense mediastinal fibrosis that seriously restricted motion and function of the heart, great vessels, and bronchi.

Table 40-1 illustrates the radiation tolerance of various organs, based on experience with 1 million volt x-rays employed in the treatment

TABLE 40-1.—TOLERANCE DOSES OF RADIATION FOR VARIOUS NORMAL ORGANS

Organ	Dose (delivered in 50 days), rads
Stomach	4,000
Transverse colon	4,500
Small intestine	4,500
Spinal cord	5,000
Kidney	5,000

of testicular tumors through opposing portals. The betatron, with energies up to 22 mev,

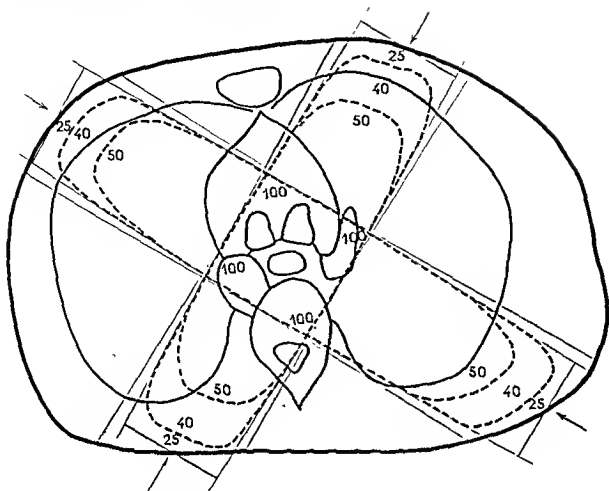


Fig. 40-2. Distribution of dose in the treatment of carcinoma of the esophagus with a 22 mev betatron using four cross-firing portals. The 100 per cent dosage is nicely distributed in the region of the esophagus. However, the heart and portions of the lungs, situated in the four zones between the 50 per cent and 100 per cent isodose lines, are subjected to intense irradiation. This could be minimized by employing a rotation technic. (Courtesy Professor M. Tubiano)

produces rays of such great penetration that the maximum surface dose is situated 40 mm. below the skin surface. At first glance it appears that the undesirable intense irradiation of the subcutaneous tissues has been overcome. However, the magnitude of the exit dose produced by the beam of betatron x-rays emerging through the opposite side of the body is often increased to a point where there is considerable unwanted radiation in the tissues on the far side of the tumor (Figure 40-2). In carcinoma of the esophagus, this disadvantage is of no practical importance. In the head and neck, where the cross-section area is small, a very large dose is delivered to the subcutaneous tissues at the exit side of the beam, producing similar complications to those encountered with the incident beam from 1 to 2 mev x-rays (see Vol. 1, Chap. 20).

Because of the high morbidity when attempting to deliver large doses to a deeply situated tumor through a single portal or two opposing portals, these portal arrangements should be abandoned except for a few special situations.

In order to avoid severe injuries to normal thoracic structures, treatment planning entails either multiple portals or the logical outgrowth of the multiple portal technic, namely, supervoltage rotation irradiation.

The use of rotation technics with supervoltage x-ray apparatuses has produced patterns of dose distributions throughout the body that are theoretically and practically superior to patterns obtained with 180 kv to 250 kv radiation, i.e., a high homogeneous dose throughout the tumor-bearing region and a low dose in the normal tissues [4, 7].

In order to obtain efficiency in the application of these high energy rays, there must be two additional factors: (1) an adequate distance between the source of radiation and the skin (more than 85 cm.) in order that the inverse square law operate effectively, and (2) an adequate collimation (beam-shaping) device to minimize side scatter of soft secondary radiation outside the geometric confines of the beam. Unfortunately, the beam of radiation that emerges from the relatively large focal spot of most cobalt-60 teletherapy machines is poorly defined and a large penumbra of un-

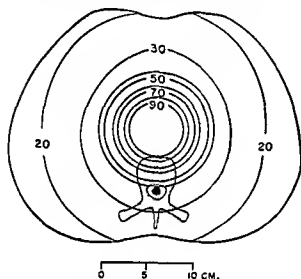


Fig. 40-3. Dose distribution in rotation therapy for carcinoma of the esophagus using 2 mev x-rays with a field size of 6×15 cm. The distance between the 90 per cent and 50 per cent isodose lines is only 1.8 cm. with this field size. This rapid fall-off in dosage from the tumor zone to the normal tissue zone is due to the long target-axis distance and to good collimation of the x-ray beam.

desirable radiation spills over into the adjacent normal tissues. This phenomenon is less marked with the smaller focal spot of supervoltage x-ray machines.

Large cobalt bombs, with sources of 3,000 curies or more, used at a source-to-skin distance of 85 cm. or more and with efficient collimation, provide a type of supervoltage therapy comparable to that of x-ray machines operating at a peak voltage of 2 mev to 3 mev.

Small cobalt bombs of 1,000 curies or less, operating at distances of less than 50 cm. and with poor collimation, do not provide any of the advantages of supervoltage radiation with the possible exception of some skin-sparing effect.

Figure 40-3 demonstrates typical rotational isodose curves for a well-collimated 2 mev x-ray machine. Note the high index of efficiency of the radiation technic in that there is a rapid fall-off in the intensity of radiation from the 90 per cent to the 50 per cent isodose line. The former line is used to represent the limits of the high dosage volume and the latter, the beginning of the low dosage region in normal tissues.

In the treatment of carcinoma of the esophagus with a 6 cm. diameter field, the distance between the 90 per cent and 50 per cent isodose lines is only 1.8 cm. when treatment is carried out with a 2 mev x-ray machine; while with a poorly collimated cobalt bomb this distance is over 3 cm. For example: with a 2 mev x-ray machine when the tumor dose to the esophagus is 5,000 rads, the spinal cord would receive a dose of only 1,950 rads, while with the cobalt source, the dose to the spinal cord would be approximately 2,800 rads.

In effect, a poorly collimated cobalt bomb operated at a short source-to-skin distance offers little advantage in rotation therapy over a 250 kv x-ray machine from the standpoint of effect on the tumor.

TECHNIC OF SUPERVOLTAGE ROTATION IRRADIATION

TOPOGRAPHIC PROJECTION OF ANATOMIC LOCATION OF THE TUMOR ONTO THE SKIN OF THE CHEST WALL

The diagnostic radiographs are reviewed in order to approximate the location of the tumor. A note is made of any displacement or atypical position of the esophagus. These radiographs are of little value for accurate beam-aiming purposes as their exclusive employment leads to errors in aiming the beam of radiation, sometimes completely missing the tumor. They have usually been made with the patient in a position different from that during treatment.

The patient is taken to the fluoroscopic room and seated in the proposed treatment position. With the aid of contrast medium, the patient is positioned so that the long axis of the tumor occupies a vertical plane. The superior and inferior margins of the tumor are now marked in ink on the anterior chest. The

patient is reversed and similar marks are placed posteriorly. The lights are then turned on in the fluoroscopic room and a permanent mark is placed on the skin anteriorly and posteriorly to identify the middle of the tumor. Two large metal rings, one of 6 cm. and the other of 8 cm. diameter, are fastened front and back with the lower edges of the rings touching the permanent reference marks. These rings have two purposes. The smaller

designate the transverse axis of the chest. Radiographs are now taken in anteroposterior and lateral projections. The patient must still be maintained in the proposed treatment posture. In the anteroposterior view, the front or back ring can be identified by the variation in size, should it be necessary to adjust its position. With the reference marks and rings undisturbed, the patient is now returned to the supervoltage room for a port film.



Fig. 40-4. Supervoltage (2 mev) chest film with anterior and posterior ring markers in position. The soft-tissue mass of the esophageal tumor can be seen displacing and compressing the trachea.

ring is anterior, the larger ring posterior, for proper identification of the two reference marks in the anteroposterior projection. They also serve as a basis for determining the distortion factor for the individual x-ray films. Occasionally, for anatomic reasons, the rings are positioned so that the reference mark is at the center instead of the edge of the ring.

The patient is refluoroscoped in the lateral position to check the horizontal alignment of the rings with the center of the tumor and to see that this line is perpendicular to the axis of the proposed cylinder of rotation. At the same time, other marks are placed on the skin over both sides of the lateral chest to

PORT FILMS

The 2 mev resonant transformer generator has a well-collimated beam and a relatively small focal spot (1.3 cm. diameter) so as to yield satisfactory radiographs. Of the lateral position, a double exposure portal film is taken. For the first exposure, the beam is the size of the treatment portal at the axis of rotation. For the second exposure, the shutters are opened to maximum portal size. If the esophagus is displaced sideways from normal position, an additional anteroposterior port film is made. The films are immediately developed and studied for accuracy of beam alignment (Figure 40-4). These port films

constitute the most important step in accurate beam alignment.

CONTOUR AND DOSE CALCULATION

A contour of the patient is now made with a contourmeter. The tumor-air ratio and dosage are calculated according to the method previously described [4]. The patient is seated on the rotation platform and fastened in position.

were treated with 2 mev x-rays, rotation technique, at the Hospital for Joint Diseases (New York). There were thirty-three men and seven women, with ages ranging from forty-three to seventy-six years, the average age being sixty years. The duration of disease, from the onset of symptoms to the first x-ray treatment, ranged from two weeks to twenty-eight months, with an average elapsed time of 4.7 months.



Fig. 40-5 An extensive carcinoma of the esophagus with a palpable supraclavicular node. (Left) Radiograph taken before treatment. (Right) Radiograph taken immediately following a tumor dose of 9,000 rads in 39 days using 2 mev rotation therapy. The supraclavicular node was incorporated in the cylinder of intense irradiation, which measured 8 cm diameter and 17 cm. long. One year later there was only slight evidence of radiation fibrosis of normal lung tissue.

The cumbersome back pointer is not employed. At each setup the Dresner front pointer is aligned with each of the four marks on the skin, which are supposed to be 90 degrees apart. This takes from one to two minutes. The size of the treatment portal is determined at the axis of rotation and ranges from 4 to 8 cm. in width and from 7 to 23 cm. in length. The patient is now ready for treatment.

CLINICAL MATERIAL

From January 1, 1952, to January 1, 1957, forty patients with carcinoma of the esophagus

Thirty-five of the lesions were verified histologically. In the remaining five patients, biopsy could not be obtained owing to technical difficulties or to the extreme weakness of the patient.

No patient was refused treatment, and in spite of the debilitated condition of many of the patients on admission, the majority withstood the treatment program well. Only three patients were unable to tolerate a tumor dose of 5,000 r or more. Of the forty patients, sixteen had distant metastases to the supraclavicular or abdominal nodes, and two had demonstrable tracheobronchial invasions. Four

patients who were explored surgically had advanced local cancer with regional metastases, and biopsy only was performed. Two patients had had previous resection for carcinoma of the lower third of the esophagus, five years and one year, respectively, prior to referral for irradiation for recurrences. To summarize: these patients had advanced cancer of the esophagus, often preterminal.

The distribution of the neoplasms was as follows: upper third, eleven; middle third, twenty-two; lower third, seven. Tumors arising in the cardia of the stomach and those in the epiesophageal group [10] were excluded.

The length of the cancers, measured radiographically, ranged from 4 to 20 cm., with an average length of 7.8 cm.

TUMOR DOSE

The tumor doses ranged from 3,000 rads in 18 days to 9,800 rads in 58 days. The average tumor dose was 7,000 rads in 40 days. The modal dose was approximately 8,000 rads in 42 days. The comparatively high dosage level was selected because post-mortem examinations had shown persistent carcinoma following irradiation with doses up to 6,000 rads.

RESULTS

The early symptomatic improvement following treatment was encouraging. Relief of dysphagia and pain was almost universal, and 47 per cent of the patients were restored to an unrestricted diet. The number of patients with radiographic evidence of moderate or marked tumor shrinkage was large. There was complete radiographic disappearance of the neoplasm in 32 per cent of the patients (Figure 40-5). Tables 40-2 and 40-3 show the immediate response of the tumor in terms of the patient's eating ability and radiographic appearance of the esophagus in the first or second months following treatment. A comparison is made with similar responses in Krebs' series [9].

Of the 40 patients treated, 29 died in periods of from 2 to 21 months; 7 are living from 2 to 9.5 months; and 3 were lost to follow-up after 3.5, 9, and 12 months, respectively. The average length of survival for all patients in this series was 6.3 months. The longest survival time to date was 21 months and the shortest 2 months (Figure 40-6).

The effect of the administered tumor dose on the survival pattern is illustrated in Figure

TABLE 40-2.—EATING ABILITY AT THE END OF TREATMENT

Diet	Authors' Series		Krebs [9]	
	Number of patients	Per cent	Number of patients	Per cent
Unrestricted	19	47	77	35
Unrestricted except for chopped meats	8	20	26	12
Pureed food	8	20	50	23
Liquids	4	10	60	28
Complete obstruction	1	3	4	2

TABLE 40-3.—IMMEDIATE RADIOGRAPHIC RESULTS AT THE END OF TREATMENT

Response of tumor	Authors' Series		Krebs [9]	
	Number of patients	Per cent	Number of patients	Per cent
Total disappearance	13	32	42	20
Improved	17	43	96	44
Unchanged	2	5	28	13
Worse	1	3	6	3
No examination	7	17	42	20

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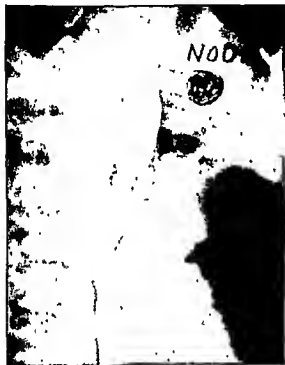


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40-7. Although the majority of patients surviving for six months or more received a tumor dose in excess of 7,000 rads, the overall survival statistics indicate that utilization of doses of this magnitude rather than 5,000 or 6,000 r offers no definite advantage. Any

of treatment to eight months after therapy. Perforation of the esophagus into the tracheobronchial tree or adjacent mediastinal structures occurred in seven (17.5 per cent). All these last patients received a dose higher than 6,000 rads.

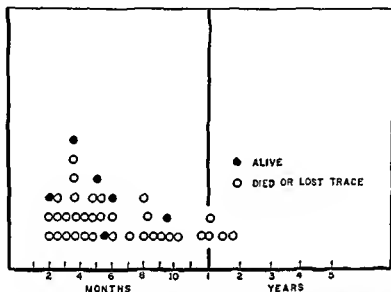


Fig. 40-6. Results in a series of 40 patients with carcinoma of the esophagus treated with 2 mev x-rays at the Hospital for Joint Diseases (New York) from January, 1952, to January, 1957. In spite of super-voltage x-rays and an efficient rotation technic, at this time no patient survived longer than two years.

increase that was obtained in the effective destruction of neoplasms was nullified by the increase in local radiation damage.

The incidence of complications following therapy in this series bears out this contention (Table 40-4). Over 90 per cent of the patients treated had some degree of resultant esophageal stenosis. This was of a sufficient degree to cause recurrent dysphagia in nine (22 per cent) of the forty patients. Persistent and recurrent esophagitis occurred in ten (25 per cent) at varying intervals from the last week

However, residual or recurrent neoplasm could be demonstrated by radiographic or post-mortem findings in only ten patients (25 per cent). Progression of the cancer outside the treatment field, including local and distant metastases, was observed in thirteen patients (33 per cent).

At the present time, the best five-year survival rate is that reported by Gynning [5], using 180 kv x-rays with rotation. In a series of eighty-eight patients treated, five survived for five years.

TABLE 40-4.—FAILURES AND COMPLICATIONS

	Number of Patients	Per cent
Persistent local esophageal cancer	7	17.5
Local recurrence (in region of treatment)	3	7.5
Recurrence above or below region of treatment	2	5.0
Progressive distant metastases	13	33.0
Persistent or recurrent esophagitis	10	25.0
Esophageal perforation	7	17.5
Stenosis of sufficient degree to cause recurrent dysphagia	9	22.0

The early figures of several series treated with 2 mev to 23 mev x-rays and with cobalt-60 teletherapy showed no obvious increase in the over-all survival rates. Blomfield [2] treated twenty-eight patients with 2 mev x-rays and reported two three-year survivors. Haas and Harvey [6] treated eighteen patients with a 23 mev betatron and had one two-year sur-

tients with this cancer.

In the treatment of a neoplasm, the lower limit of the range of dosage selected is determined by the radiosensitivity of the type of tumor. The upper limit is dictated by the tolerance of the normal tissues. Seaman and Ackerman [14], in a study of the effects of 24 mev x-rays on the normal esophagus during

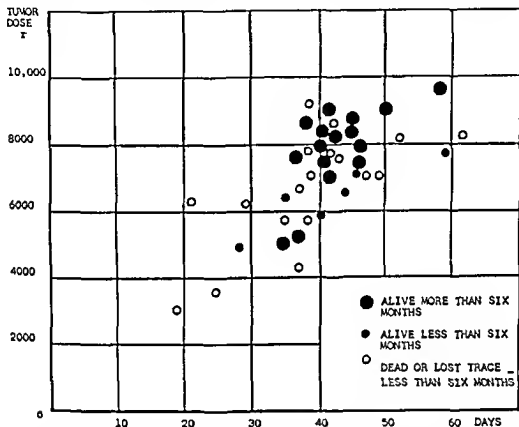


Fig 40-7. Doses employed in 40 patients treated with 2 mev rotation irradiation. The large black dots represent those patients who survived more than six months following treatment. The smaller black dots represent those alive at the present time who had not yet reached the six-month interval. The white circles represent patients who either died or were lost to follow up within the six-month period following treatment. With this irradiation technique, larger than usual tumor doses could be delivered. However, they did not improve the results.

vivor to date. Bernard [12] treated forty-six patients with a betatron and had six one-year survivors. Lott and Smith [11] treated sixty-eight patients with cobalt 60, using both multiple portal and rotation techniques, with tumor doses ranging from 5,800 r to 6,800 r in three to five weeks. Six patients have survived for three years or more without apparent local recurrence.

It seems apparent that increasing the energy of the radiation to still higher levels will probably not significantly increase survival of pa-

treatment of lung carcinoma, demonstrated that the tolerance dose for this organ is in the neighborhood of 6,000 rads given at the rate of about 1,000 rads per week. It seems evident that only a certain percentage of carcinomas in the esophagus can be destroyed with 5,000 to 6,000 rads, but to destroy a greater percentage of neoplasms by utilizing higher doses causes increased radiation injury and often fatal complications. The results of this series indicate that for the majority of patients no real increase in survival can be

expected if eradication of the neoplasm necessitates dosages much in excess of normal tissue tolerance.

For many patients, it seems evident that elective gastrostomy prior to irradiation is a necessary step to maintain nutrition and decrease the severity of esophagitis during and

after the course of treatment. Until the esophagus has had time to recover from the double insult of neoplastic invasion and subsequent heavy irradiation, many months may pass and it is in this critical period that adequate "aftercare" may eventually add to the present short list of survivors.

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